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Invention: CHEMICAL COMPOUNDS

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- ☐ Regular Utility Application
- ☐ Continuing Application
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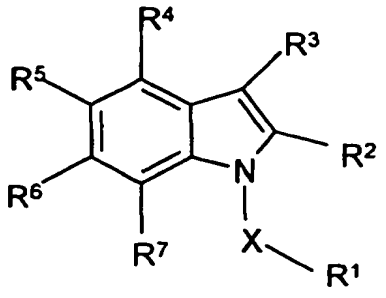

(I)

(57) Abstract: The use of a 3-substituted indole compound of formula (I) or a pharmaceutically acceptable salt, amide or ester thereof; X is CH_2 or SO_2 and R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are certain specified organic moieties, for use in the preparation of a medicament for the inhibition of monocyte chemoattractant protein-1 and/or RANTES induced chemotaxis. Pharmaceutical compositions containing certain compounds of formula (I) and novel compounds of formula (I) are also described and claimed.

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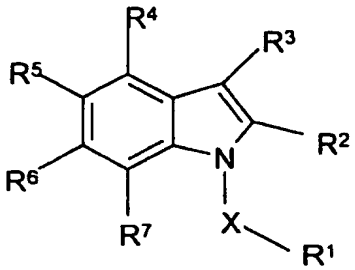

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The use of a 3–substituted indole compound of formula (I) or a pharmaceutically acceptable salt, amide or ester thereof; X is CH_2 or SO_2 and R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are certain specified organic moieties, for use in the preparation of a medicament for the inhibition of monocyte chemoattractant protein–1 and/or RANTES induced chemotaxis. Pharmaceutical compositions containing certain compounds of formula (I) and novel compounds of formula (I) are also described and claimed.

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CHEMICAL COMPOUNDS

The present invention relates to chemical compounds, to their production as well as to pharmaceutical compositions containing them as well as to their use in therapy, in particular of inflammatory disease.

MCP-1 is a member of the chemokine family of pro-inflammatory cytokines which mediate leukocyte chemotaxis and activation. MCP-1 is a C-C chemokine which is one of the most potent and selective T-cell and monocyte chemoattractant and activating agents known. MCP-1 has been implicated in the pathophysiology of a large number of inflammatory diseases including rheumatoid arthritis, glomerular nephritides, lung fibrosis, restenosis (International Patent Application WO 94/09128), alveolitis (Jones et al., 1992, *J. Immunol.*, **149**, 2147) and asthma. Other disease areas where MCP-1 is thought to play a part in their pathology are atherosclerosis (e.g. Koch et al., 1992, *J. Clin. Invest.*, **90**, 772 -779), psoriasis (Deleuran et al., 1996, *J. Dermatological Science*, **13**,. 228-236), delayed-type hypersensitivity reactions of the skin, inflammatory bowel disease (Grimm et al., 1996, *J. Leukocyte Biol.*, **59**,. 804-812), multiple sclerosis and brain trauma (Berman et al, 1996, *J. Immunol.*, **156**,. 3017-3023). An MCP-1 inhibitor may also be useful to treat stroke, reperfusion injury, ischemia, myocardial infarction and transplant rejection.

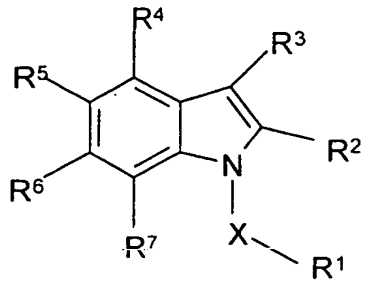
MCP-1 acts through the MCP-1 receptor (also known as the CCR2 receptor). MCP-2 and MCP-3 may also act, at least in part, through the MCP-1 receptor. Therefore in this specification, when reference is made to "inhibition or antagonism of MCP-1" or "MCP-1 mediated effects" this includes inhibition or antagonism of MCP-2 and/or MCP-3 mediated effects when MCP-2 and/or MCP-3 are acting through the MCP-1 receptor.

Copending International Patent Application Nos. PCT/GB98/02340 and PCT/GB98/02341 describe and claim groups of compounds based upon the indole ring structure which are inhibitors of MCP-1 and therefore have applications in therapy.

The use of certain indole derivatives as NMDA antagonists is described is USP5051442, WO9312780, EP-483881. Other indoles and their use as inhibitors of leukotriene biosynthesis is described in for example, EP-A- 275-667.

The applicants have found a particular substitution on the indole ring produces advantageous results when used therapeutically as inhibitors of MCP-1.

According to the present invention there is provided the use of a compound of formula (I)

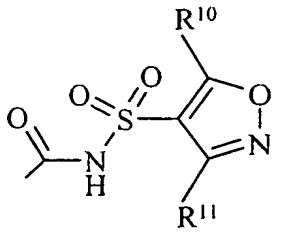


(I)

X is CH_2 or SO_2

R^1 is an optionally substituted aryl or heteroaryl ring;

R^2 is carboxy, cyano, $-C(O)CH_2OH$, $-CONHR^8$, $-SO_2NHR^9$, tetrazol-5-yl, SO_3H, or a group of formula (VI)



(VI)

where R^8 is selected from hydrogen, alkyl, aryl, cyano, hydroxy, $-SO_2R^{12}$ where R^{12} is alkyl, aryl, heteroaryl, or haloalkyl, or R^8 is a group $-(CHR^{13})_r-COOH$ where r is an integer of 1-3 and each R^{13} group is independently selected from hydrogen or alkyl; R^9 is hydrogen, alkyl, optionally substituted aryl such as optionally substituted phenyl or optionally subtituted heteroaryl such as 5 or 6 membered heteroaryl groups, or a group COR^{14} where R^{14} is alkyl, aryl, heteroaryl or haloalkyl; R^{10} and R^{11} are independently selected from hydrogen or alkyl, particularly C_{1-4} alkyl;

R^3 is a group OR^{15}, $S(O)_qR^{15}$, $NHCOR^{16}$, $NHSO_2R^{16}$, $(CH_2)_sCOOH$, $(CH_2)_tCONR^{17}R^{18}$, $NR^{17}R^{18}$, $SO_2NR^{17}R^{18}$ or optionally substituted alkenyl, where q is 0, 1 or 2, s is 0 or an integer of from 1 to 4, t is 0 or an integer of from 1 to 4, R^{15} is a substituted alkyl or cycloalkyl group or an optionally substituted heteroaryl group , R^{16} is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl and R^{17} and R^{18} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl and optionally substituted heteroaryl, with the proviso that at least one of R^{17} or R^{18} is other than hydrogen, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms; and

R^4, R^5, R^6 and R^7 are independently selected from hydrogen, a functional group or an optionally substituted hydrocarbyl groups or optionally substituted heterocyclic groups: for use in the preparation of a medicament for the inhibition of monocyte chemoattractant protein-1 and/or RANTES induced chemotaxis.

Pharmaceutically acceptable salts, esters and amides of compounds of formula (I) may also be used in this way.

In particular in the above formula s is an integer of from 1 to 4.

Suitably R^4 is other than a group $OR^{18'}$, $S(O)_mR^{18'}$, $NR^{19}R^{20}$, $C(O)NR^{19}R^{20}$, $NHCOR^{18}$, $NHSO_2R^{18}$or $OCONR^{19}R^{20}$ or an alkyl group substituted by OR^{18}, $S(O)_mR^{18}$, $NR^{19}R^{20}$ where R^{18}, R^{19}, R^{20} and m are as defined hereinafter and $R^{18'}$ is a substituted hydrogen-containing alkyl group.

Compounds of formula (I) are inhibitors of monocyte chemoattractant protein-1. In addition, they appear to inhibit RANTES induced chemotaxis. RANTES is another chemokine from the same family as MCP-1, with a similar biological profile, but acting though the CCR1 receptor. As a result, these compounds can be used to treat disease mediated by these agents, in particular inflammatory disease. Thus the invention further provides a compound of formula (I) for use in preparation of a medicament for the treatment of inflammatory disease.

In this specification the term 'alkyl' when used either alone or as a suffix includes straight chained, branched structures. These groups may contain up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. Similarly the terms "alkenyl" and "alkynyl" refer to unsaturated straight or branched structures containing for example from 2 to 10, preferably

from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms. Terms such as "alkoxy" comprise alkyl groups as is understood in the art.

The term "halo" includes fluoro, chloro, bromo and iodo. References to aryl groups include aromatic carbocylic groups such as phenyl and naphthyl. The term "heterocyclyl" includes aromatic or non-aromatic rings, for example containing from 4 to 20, suitably from 5 to 8 ring atoms, at least one of which is a heteroatom such as oxygen, sulphur or nitrogen. Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

"Heteroaryl" refers to those groups described above which have an aromatic character. The term "aralkyl" refers to aryl substituted alkyl groups such as benzyl.

Other expressions used in the specification include "hydrocarbyl" which refers to any structure comprising carbon and hydrogen atoms. For example, these may be alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl.

The term "functional group" refers to reactive substituents. They may comprise electron-donating or electron-withdrawing. Examples of such groups include halo, cyano, nitro, $C(O)_nR^{18}$, OR^{18}, $S(O)_mR^{18}$, $NR^{19}R^{20}$, $C(O)NR^{19}R^{20}$, $OC(O)NR^{19}R^{20}$, $-NR^{19}C(O)_nR^{18}$, $-NR^{18}CONR^{19}R^{20}$, $-N=CR^{18}R^{19}$, $S(O)_nNR^{19}R^{20}$ or $-NR^{19}S(O)_nR^{18}$ where R^{18}, R^{19} and R^{20} are independently selected from hydrogen or optionally substituted hydrocarbyl, or R^{19} and R^{20} together with the atom to which they are attached, form an optionally substituted heterocyclyl ring as defined above which optionally contains further heteroatoms such as $S(O)_n$, oxygen and nitrogen, n is an integer of 1 or 2, m is 0 or an integer of 1-3.

Suitable optional substituents for hydrocarbyl groups R^{18}, R^{19} and R^{20} include halo, perhaloalkyl such as trifluoromethyl, mercapto, hydroxy, carboxy, alkoxy, heteroaryl, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyalkoxy, aryloxy (where the aryl group may be substituted by halo, nitro, or hydroxy), cyano, nitro, amino, mono- or di-alkyl amino, oximino or $S(O)_m$ where m is as defined above.

Where R^{19} and R^{20} together form a heterocyclic group, this may be optionally substituted by hydrocarbyl such as alkyl as well as those substituents listed above for hydrocarbyl groups R^{18}, R^{19} and R^{20}.

Suitable substituents for hydrocarbyl or heterocylic groups R^5, R^6 and R^7 include those listed above for R^{18}, R^{19} and R^{20}.

Suitably R^1 is an optionally substituted phenyl, pyridyl, naphthyl, furyl or thienyl ring, and in particular is a substituted phenyl or pyridyl ring.

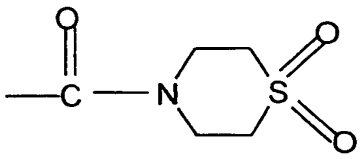
Suitable optional substitutents for R^1 in formula (I) include alkyl, alkenyl, alkynyl, halo, haloalkyl including perhaloalkyl such as trifluoromethyl, mercapto, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, hydroxyalkoxy, alkoxyalkoxy, alkanoyl, alkanoyloxy, cyano, nitro, amino, mono- or di-alkyl amino, oximino, sulphonamido, carbamoyl, mono or dialkylcarbamoyl or $S(O)_m R^{21}$ where m is as defined above and R^{21} is hydrocarbyl.

Suitably R^4 is selected from hydrogen, hydroxy, halo, alkoxy, aryloxy or an optionally substituted hydrocarbyl group or optionally substituted heterocyclic group.

Particular examples of substituents R^4 include hydrogen, hydroxy, halo, optionally substituted alkyl such as aralkyl, carboxyalkyl or the amide derivative thereof, alkoxy, or aryloxy.

Most preferably R^4 is hydrogen.

Particular examples of substituents R^5, R^6 and R^7 include hydrogen, hydroxy, halo, optionally substituted alkyl such as aralkyl, carboxyalkyl or the amide derivative thereof; alkoxy; aryloxy; aralkyloxy; or an amino group which is optionally substituted with alkyl, aryl or aralkyl. A specific functional group which is suitable for R^5, R^6 and/or R^7 is a group of sub-formula (IV).



(IV)

Particular examples of groups R^5, R^6 and R^7 are hydrogen, hydroxy, halo or alkoxy. In particular R^6 and R^7 are hydrogen. R^5 may be hydrogen but in addition are suitably a small subsitutent such as hydroxy, halo or methoxy.

Particular substituents for R^1 include trifluoromethyl, C_{1-4}alkyl, halo, trifluoromethoxy, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, nitro, carbamoyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, sulphonamido,

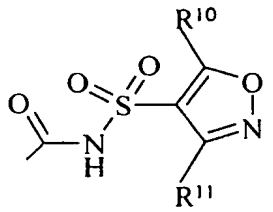
carbamoylC_{1-4}alkyl, *N*-(C_{1-4}alkyl)carbamoylC_{1-4}alkyl, *N*-(C_{1-4}alkyl)$_2$carbamoyl-C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.

Additionally or alternatively, two such substituents together may form a divalent radical of the formula -O(CH_2)$_{1-4}$O- attached to adjacent carbon atoms on the R^1 ring.

Preferred substitutents for R^1 are one or more non-polar substituents such as halo.

In particular, R^1 is substituted by one or more halo groups, in particular chlorine. A particular example of an R^1 group is 3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 3-chloro-4-fluorophenyl or 2,3-dichloropyrid-5-yl.

Examples of groups R^2 include carboxy; cyano; tetrazol-5-yl; SO_3H; -$CONHR^8$ where R^8 is selected from cyano, hydroxy, -SO_2R^{12} where R^{12} is alkyl such as C_{1-4} alkyl, aryl such as phenyl, heteroaryl or trifluoromethyl, or R^8 is a group-(CHR^{10})$_r$-COOH where r is an integer of 1-3 and each R^{10} group is independently selected from hydrogen or alkyl such as C_{1-4} alkyl; or R^2 is a group -SO_2NHR^9 where R^9 is an optionally substituted phenyl or an optionally substituted 5 or 6 membered heteroaryl group, or a group COR^{14} where R^{14} is alkyl such as C_{1-4} alkyl, aryl such as phenyl, heteroaryl or trifluoromethyl, or R^2 is a group of formula (VI)



(VI)

where R^{10} and R^{11} are independently selected from hydrogen or alkyl, particularly C_{1-4} alkyl.

Preferably R^2 is carboxy or a pharmaceutically acceptable salt or ester thereof.

Particular groups R^3 include OR^{15}, $S(O)_qR^{15}$, $NHCOR^{16}$, $NHSO_2R^{16}$, $SO_2NR^{17}R^{18}$ where q, R^{15}, R^{16}, R^{17} and R^{18} are as defined above.

Suitable optional substitutents for the group R^{15}, R^{16}, R^{17} and R^{18} as they appear in the definition of R^3, or alkenyl groups R^3 as defined above include functional groups as hereinbefore defined, as well as aryl or heteroaryl groups, either of which may themselves be substituted by one or more functional groups.

Particular examples of substituents for groups R^{15}, R^{16}, R^{17} and R^{18} include one or more groups selected from halo such as chloro, hydroxy, cyano, amino, mono- or di-

alkylamino, C_{1-4} alkoxy, carboxy, sulphonamido, $CONH_2$, morpholino, pyridyl, pyrimidinyl, phenyl optionally substituted by halo such as chloro, carboxy, hydroxy, alkoxy such as methoxy, carbamoyl, acyl such as acetyl, or hydroxyalkyl where the alkyl group suitably includes at least two carbon atoms, such as hydroxyethyl.

Where R^{15}, R^{16}, R^{17} and R^{18} is a heteroaryl group, or where R^{17} and R^{18} together form an optionally substituted heterocyclic ring, these may be substituted by functional groups, or by alkyl groups such as methyl or ethyl, or alkenyl or alkynyl groups any of which may be subsituted, for example with hydroxy.

A preferred group for R^3 is a group OR^{15} straight or branched chain alkyl group which carries at least one hydroxy group, for example or 2 hydroxy groups. Other substituents, as defined above, may be provided on the alkyl chain.

Preferably R^3 is a group of formula $-O(CH_2)_a[(CHOH)(CH_2)_b]_d CH_2OH$ where a is 0 or an integer of from 1 to 4, b is 0 or an integer of from 1 to 3, and d is 0, or 1.

Examples of such R^3 include $OCH_2CHOHCH_2OH$ and OCH_2CH_2OH.

X is CH_2 or SO_2 and is preferably CH_2.

Suitable pharmaceutically acceptable salts of compounds of formula (I) include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N*,*N*-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically acceptable salt is a sodium salt.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically acceptable esters for carboxy include alkyl esters, such as C_{1-6} alkyl esters for example, ethyl esters, C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxy-carbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example

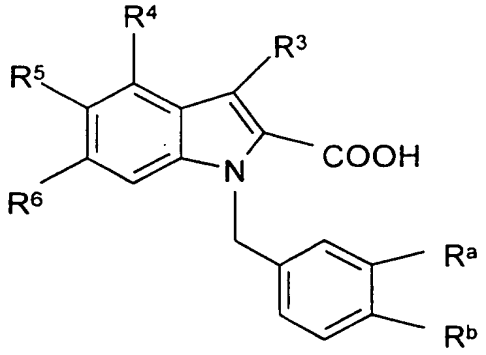
5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

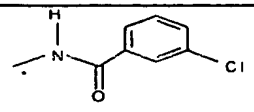
Suitable pharmaceutically acceptable esters of compounds of formula (I) are *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

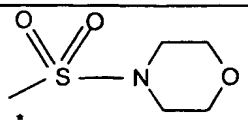
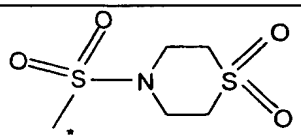
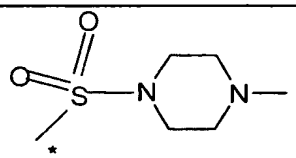
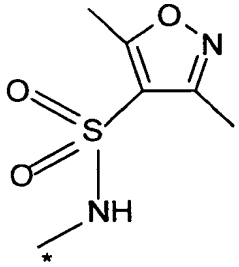
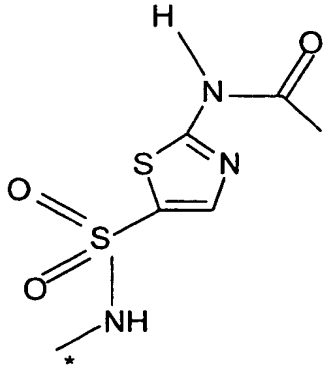
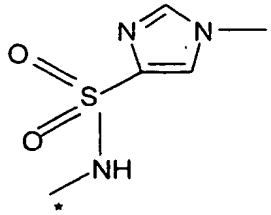
Esters which are not *in vivo* hydrolysable are useful as intermediates in the production of the compounds of formula (I) and therefore these form a further aspect of the invention.

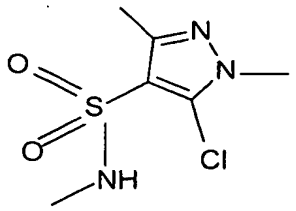
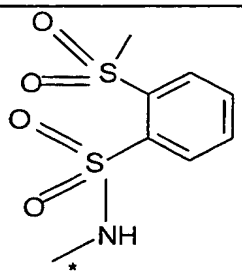
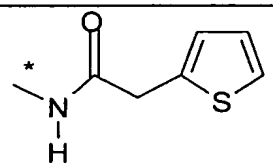
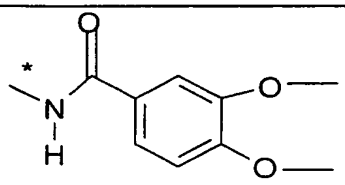
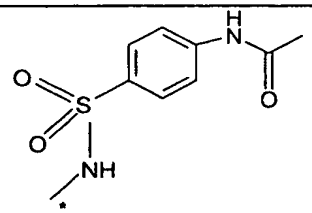
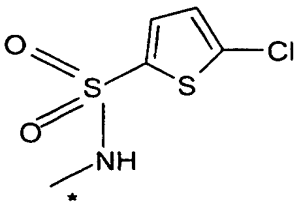
Thus examples of compounds of formula (I) include the following:

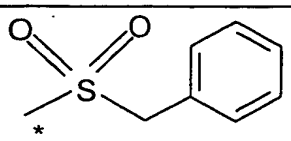
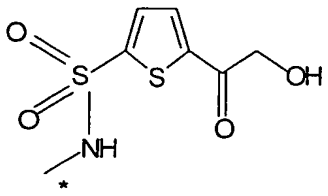
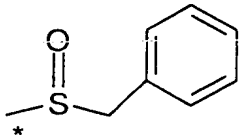
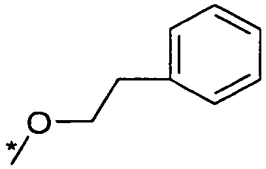
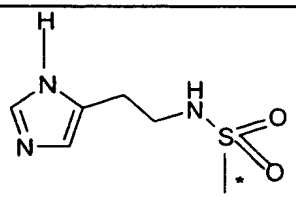
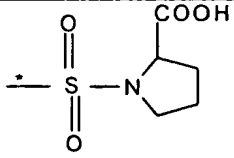
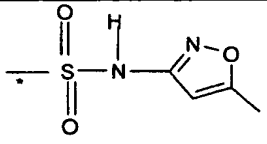
Table 1

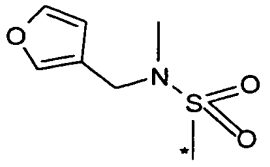
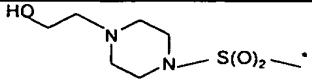
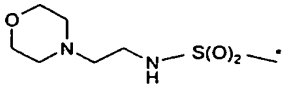
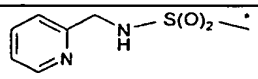
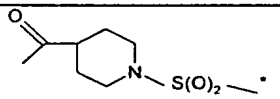
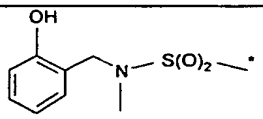
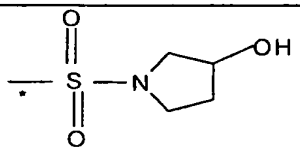
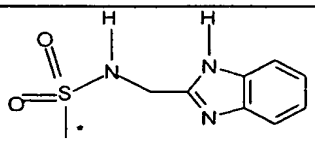
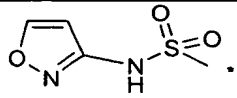
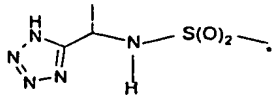
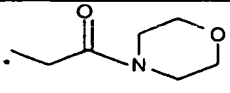


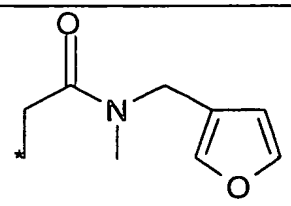
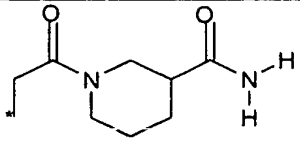
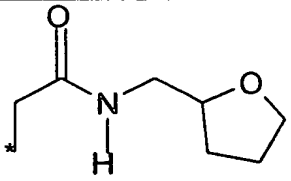
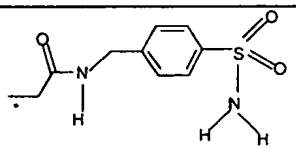
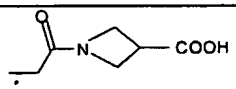
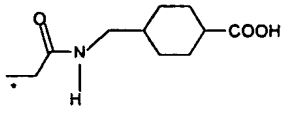
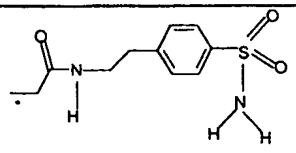
Compd No.	R^3	R^4	R^5	R^6	R^a	R^b
1		H	H	H	Cl	Cl

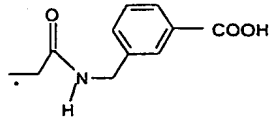
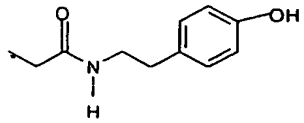
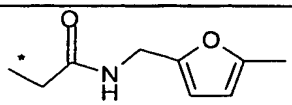
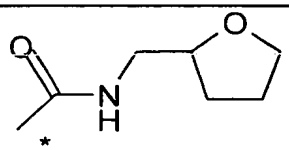
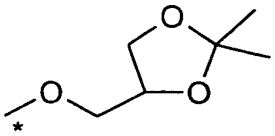
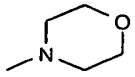
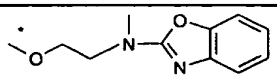
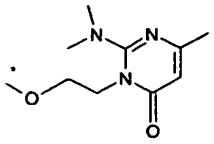
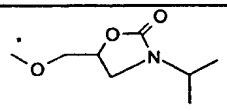
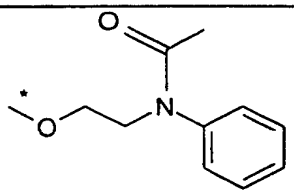
2	$-NHS(O)_2CH_3$	H	H	H	Cl	Cl
3		H	H	H	Cl	Cl
4		H	H	H	Cl	Cl
5	$-SCH_2(C_6H_5)$	H	H	H	Cl	Cl
6		H	H	H	Cl	Cl
7	$S(O)_2N(CH_2)_2NH_2$	H	H	H	Cl	Cl
8		H	H	H	Cl	Cl
9		H	H	H	Cl	Cl
10		H	H	H	Cl	Cl
11	$NHS(O)_2CH_2COOH$	H	H	H	Cl	Cl

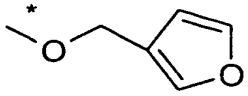
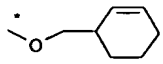
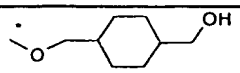
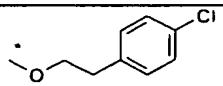
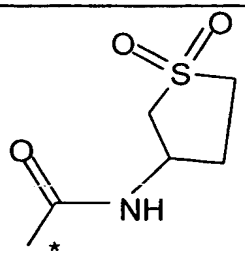
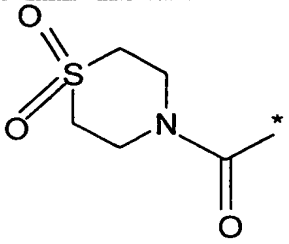
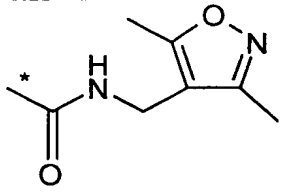
12		H	H	H	Cl	Cl
13		H	H	H	Cl	Cl
14	$NHC(O)CH_2COOH$	H	H	H	Cl	Cl
15	$NHC(O)CH_2CH_2OCH_3$	H	H	H	Cl	Cl
16		H	H	H	Cl	Cl
17	$NHC(O)CH(OH)CH_3$	H	H	H	Cl	Cl
18		H	H	H	Cl	Cl
19		H	H	H	Cl	Cl
20		H	H	H	Cl	Cl

21		H	H	H	Cl	Cl
22		H	H	H	Cl	Cl
23	OCH_2CH_2OH	H	H	H	Cl	Cl
24	$SCH_2C(O)_2H$	H	H	H	Cl	Cl
25		H	H	H	Cl	Cl
26		H	H	H	Cl	Cl
27	OCH_2COOH	H	H	H	Cl	Cl
28	CH_2COOH	H	H	H	Cl	Cl
29	$S(O_2)NH(CH_2)_2OH$	H	H	H	Cl	Cl
30	$S(O_2)N((CH_2)_2OH)_2$	H	H	H	Cl	Cl
31		H	H	H	Cl	Cl
32		H	H	H	Cl	Cl
33		H	H	H	Cl	Cl

34		H	H	H	Cl	Cl
35		H	H	H	Cl	Cl
36		H	H	H	Cl	Cl
37		H	H	H	Cl	Cl
38	$S(O)_2NHCH_2CH(OCH_3)_2$	H	H	H	Cl	Cl
39	$S(O)_2NHCH_2C{\equiv}CH$	H	H	H	Cl	Cl
40	$S(O)_2N((CH_2)_2OCH_3)_2$	H	H	H	Cl	Cl
41		H	H	H	Cl	Cl
42		H	H	H	Cl	Cl
43		H	H	H	Cl	Cl
44		H	H	H	Cl	Cl
45		H	H	H	Cl	Cl
46		H	H	H	Cl	Cl
47	$S(O)_2NH(CH_2)_2NS(O)_2N(CH_3)_2$	H	H	H	Cl	Cl
48		H	H	H	Cl	Cl

49	$CH_2C(O)NHCH_2CH_2OH$	H	H	H	Cl	Cl
50	CH=CHCOOH	H	H	H	Cl	Cl
51	$S(O)_2CH_2COOH$	H	H	H	Cl	Cl
52	$CH_2C(O)N(CH_3)$-$(CH_2)_2OH$	H	H	H	Cl	Cl
53		H	H	H	Cl	Cl
54		H	H	H	Cl	Cl
55	$CH_2C(O)N(CH_2CH_2OCH_3)_2$	H	H	H	Cl	Cl
56	$CH_2C(O)NHCH_2CH_2OCH_3$	H	H	H	Cl	Cl
57		H	H	H	Cl	Cl
58		H	H	H	Cl	Cl
59		H	H	H	Cl	Cl
60		H	H	H	Cl	Cl
61		H	H	H	Cl	Cl
62	$CH_2C(O)NHCH_2C(O)(CH_2)_2COO$ H	H	H	H	Cl	Cl

63		H	H	H	Cl	Cl
64		H	H	H	Cl	Cl
65		H	H	H	Cl	Cl
66	$O(CH_2)_2OCH_3$	H	H	H	Cl	Cl
67	$OCH_2CH_2NHC(O)OC(CH_3)_3$	H	H	H	Cl	Cl
68		H	H	H	Cl	Cl
69	$OCH_2CH_2NH_2$	H	H	H	Cl	Cl
70		H	H	H	Cl	Cl
71	$OCH_2CHOHCH_2OH$	H	H	H	Cl	Cl
72		H	H	H	Cl	Cl
73		H	H	H	Cl	Cl
74		H	H	H	Cl	Cl
75		H	H	H	Cl	Cl
76		H	H	H	Cl	Cl

77		H	H	H	Cl	Cl
78		H	H	H	Cl	Cl
79		H	H	H	Cl	Cl
80		H	H	H	Cl	Cl
81		H	H	H	Cl	Cl
82	$OCH_2CH_2OCH_2CH_3$	H	OCH_3	H	Cl	Cl
83	OCH_2CH_2OH	H	OCH_3	H	Cl	Cl
84		H	H	H	Cl	Cl
85		H	H	H	Cl	Cl
86	COOH	H	H	H	Cl	Cl

where * indicates the point of attachment of the group to the indole ring.

Some compounds of formula (I) have not been proposed hitherto for use as pharmaceuticals. Thus a further aspect of the invention provides a compound for use in therapy, said compound comprising a compound of formula (1A) which is a compound of formula (I) as defined above subject to the following provisos:

(i) when R^2 is carboxy or a salt or amide thereof, at least three of R^4, R^5, R^6 and R^7 are hydrogen, and R^3 is $S(O)qR^{15}$, R^{15} is other than C_{1-4} alkyl substituted by carboxy or an ester or amide derivative thereof;

(ii) when R^3 is a group $NHCOR^{16}$ or $NHSO_2R^{16}$, R^{16} is optionally substituted alkyl; and

(iii) where R^3 is a group SR^{14} where R^{14} is 2-quinolylmethyl, R^2 is COOH or an ethyl ester thereof, each of R^4, R^5, and R^7 are hydrogen, R^1 is 4-chlorophenyl, R^6 is other than 2-quinolylmethyl.

Yet a further aspect of the invention provides pharmaceutical compositions comprising a compound of formula (IA) as defined above.

Certain compounds of formula (I) are novel and these form a further aspect of the invention. Thus the invention further provides a compound of formula (IB) which is a compound of formula (IA) as defined above, subject to the following further provisos:

(iv) where R^3 is a group CH_2COOH, R^2 is COOH and each of R^4, R^5, R^6 and R^7 are hydrogen, R^1 is other than unsubsituted phenyl; and

(v) where R^3 is a group CH_2COOH, R^2 is COOH and each of R^4, R^5, and R^7 are hydrogen, R^1 is 4-chlorophenyl, R^6 is other than methoxy; and

(vi) when R^3 is OR^{15} or $S(O)_qR^{15}$, R^{15} is other than C_{1-6} haloalkyl.

Yet a further proviso which is suitably applied to formula (IB) is

(vii) when R^2 is $COOCH_2CH_3$, each of R^4, R^5, R^6 and R^7 are hydrogen and R^1 is 4-chlorophenyl, R^3 is other than a group $CH=CH(CN)_2$.

Furthermore, the proviso (iv') suitably applies to (IA) in that where R^3 is a group COOH, R^2 is COOH and each of R^4, R^5, R^6 and R^7 are hydrogen, R^1 is other than unsubsituted phenyl.

Particularly preferred substituents and groups on the compounds of formula (IA) and (IB) are those described above in relation to formula (I).

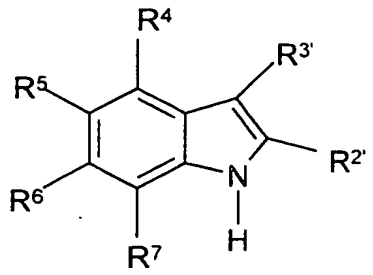
Suitable examples of compounds of formula (IB) are compounds where R^3 is a group OR^{15} straight or branched chain alkyl group which carries at least one hydroxy group, for example from 1 to 4 hydroxy groups, for example 1 or 2 hydroxy groups. Other substituents, as defined above, may be provided on the alkyl chain.

Preferably R^3 is a group of formula $-O(CH_2)_a[(CHOH)(CH_2)_b]_d CH_2OH$ where a is 0 or an integer of from 1 to 4, b is 0 or an integer of from 1 to 3, and d is 0 or 1.

Examples of such R^3 include $OCH_2CHOHCH_2OH$ and OCH_2CH_2OH.

Compounds of formula (I) are suitably prepared by methods such as those described in International Patent Application Nos. PCT/GB98/02340 and PCT/GB98/02341.

In particular compounds of formula (I) can be prepared by reacting a compound of formula (VII)



(VII)

where R^4, R^5, R^6 and R^7 are as defined in relation to formula (I), $R^{2'}$ is a group R^2 as defined in relation to formula (I) or a protected form thereof, and $R^{3'}$ is a group R^3 as defined in relation to formula (I) or a precursor thereof ; with compound of formula (VIII)

$$R^1\text{-}X\text{-}Z^1$$

(VIII)

where R^1 and X are as defined in relation to formula (I) and Z^1 is a leaving group; and thereafter if desired or necessary carrying out one or more of the following steps:

(i) changing a precursor group $R^{3'}$ to a group R^3 or a group R^3 to a different such group;

(ii) removing any protecting group from $R^{2'}$.

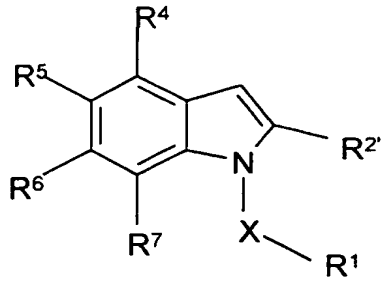
Suitable leaving groups for Z include halide such as chloride, bromide or iodide, as well as mesylate or tosylate. The reaction is suitably effected in an organic solvent such as dimethylformamide (DMF) tetrahydrofuran (THF) or DCM in the presence of a base such as sodium hydride, sodium hydroxide, potassium carbonate. Optionally the reaction is effected in the presence of a suitable phase transfer catalyst. The choice of base and solvent is interdependent to a certain extent in that certain solvents are compatible with some bases only as is understood in the art. For example, sodium hydride may preferably be used with dimethylformamide or tetrahydrofuran and sodium hydroxide is preferably used with dichloromethane and a phase transfer catalyst.

The reaction can be carried out at moderate temperatures, for example from 0 to 50°C and conveniently at about ambient temperature.

Preferably, $R^{2'}$ is an ester group in the compound of formula (VII) and this may be subsequently converted to an acid or to another ester or salt, by conventional methods. For example, when X is a group SO_2 and R^2 is a methyl ester of carboxy, it may be converted to the corresponding carboxylic acid by reaction with lithium iodide in dry pyridine or DMF.

Optional step (i) and (ii) above can be carried out using conventional methods. These will depend upon the precise nature of the groups R^3, $R^{3'}$, R^2 and $R^{2'}$ in each case. Examples of suitable reactions are illustrated hereinafter.

Alternatively, compounds of formula (I) may be prepared by reacting a compound of formula (IX)



(IX)

where X, R^1, R4, R^5, R^6 and R^7 are as defined in relation to formula (I), $R^{2'}$ is a group R^2 as defined in relation to formula (I) or a protected form thereof; with a compound of formula (X)

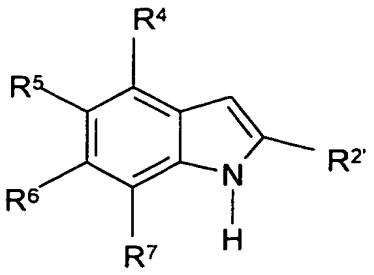
$R^{3'}$- Z^1

(X)

where $R^{3'}$ is a group R^3 as defined in relation to formula (I) or a precursor thereof ; and thereafter if desired or necessary carrying out steps (i) and/ or (ii) above.

The reaction is suitably carried out in an organic solvent which will depend upon the nature of the compound of formula (IX). Suitable leaving groups Z^1 include those listed above for Z.

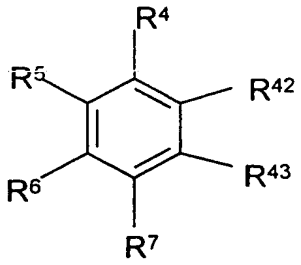
Compounds of formula (IX) may suitably be prepared by methods analogous to those described above between the compound of formula (VII) and (VIII), although in this case, a compound of formula (VIIA) will be used.



(VIIA)

In this compound, $R^{2'}$, R^4, R^5, R^6 and R^7 are as defined above.

Compounds of formula (VII) and (VIIA) may be prepared by cyclisation of a compound of formula (XI)

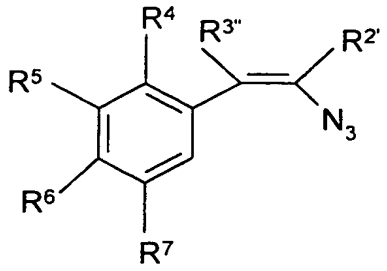


(XI)

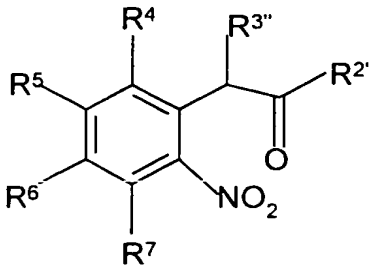
where R^4, R^5, R^6 and R^7 are as defined above and R^{42} and R^{43} represent a combination of moieties which can cyclise to form an appropriately substituted pyrrole ring. For example, R^{42} can be a group of formula $-CH=C(R^{44})N_3$ where R^{44} is a group R^2 as defined above, or a protected form thereof, and R^{43} may be hydrogen. Cyclisation to form a compound of formula (XII) may then be effected by heating for example under reflux in an organic solvent, in particular a high boiling aprotic solvent such as xylene or toluene.

Alternatively, R^{43} may be nitro and R^{42} may be a group of formula $-CH_2C(O)R^{2'}$ where $R^{2'}$ is as defined above in relation to formula (VII). These compounds will cyclise in the presence of a catalyst such as palladium on carbon in the presence of hydrogen. The reaction may be effected at moderate temperatures for example of from 0 to 80°C, conveniently at about ambient temperature.

Thus examples of compounds of formula (XI) include compounds of formula (XII) and (XIII)



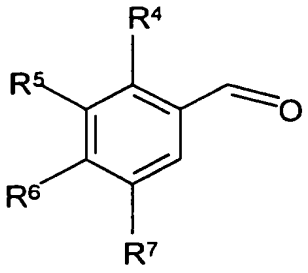
(XIII)



(XIV)

where $R^{2'}$, R^4, R^5, R^6 and R^7 are as hereinbefore defined and $R^{3''}$ is a group $R^{3'}$ or is hydrogen, which may be converted later to a group R^3 or $R^{3'}$.

Compounds of formula (XIII) where $R^{3'}$ is hydrogen may be prepared for example by reacting a compound of formula (XV)



(XV)

with a compound of formula (XVI)

$$N_3CH_2R^{2'}$$

(XVI)

where R^4, R^5, R^6, R^7, and $R^{2'}$ are as defined hereinbefore. The reaction may be effected in an organic solvent such as ethanol at low temperatures of from -20 to 0°C, suitably at about 0°C.

The reaction is suitably effected in the presence of a base such as an alkoxide, in particular an ethoxide, for example potassium ethoxide.

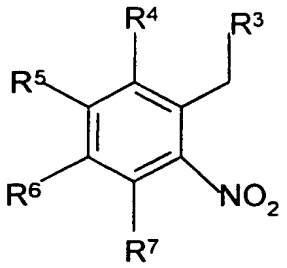
Compounds of formula (XVI) are suitably prepared by reacting a compound of formula (XVII)

$$R^{47}CH_2R^{2'}$$

(XVII)

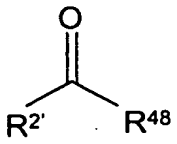
where R^3 and $R^{2'}$ are as defined above and R^{47} is a leaving group such as halide and in particular bromide, with an azide salt, such as an alkali metal azide salt in particular sodium azide.

Compounds of formula (XIV) may be prepared by reacting a compound of formula (XVIII)



(XVIII)

where R^5, R^6, R^7, R^3, R^4 and $R^{2'}$ are as defined above, with a compound of formula (XIX)



(XIX)

where $R^{2'}$ is as defined above and R^{48} leaving group such as hydroxy. Examples of compounds of formula (XVI) are oxalates such as diethyloxalate. The reaction is suitably effected in the presence of a base such as sodium hydride in an organic solvent such as THF. Moderate temperatures of from 0° to 40°C and conveniently ambient temperature is employed.

According to a further aspect of the invention there is provided a compound of the formula **(I)** as defined herein, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable

ester thereof, for use in a method of treatment of the human or animal body by therapy. In particular, the compounds are used in methods of treatment of inflammatory disease.

According to a further aspect of the present invention there is provided a method for antagonising an MCP-1 mediated effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

The invention also provides a compound of formula (I) as defined herein, or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof, for use as a medicament.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for

use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects of farnesylation of rats.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for

example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The invention is further illustrated, but not limited by the following Examples in which the following general procedures were used unless stated otherwise.

Preparation 1

Ethyl 3-bromoindole-2-carboxylate

A solution of bromine (2.72 ml) in DMF was added dropwise over 10 mins to a solution of ethyl indole-2-carboxylate in DMF. The reaction was stirred for 30 mins, then poured into water to precipitate a pale yellow solid which was filtered off and recrystallized from ethyl acetate to give the desired starting material as white needles (10.2 g, 72%), mp 150-151°; NMR d ($CDCl_3$) 1.44 (t, 3H), 4.45 (q, 2H), 7.22 (m, 1H), 7.38 (m, 2H), 7.66 (d, 1H), 9.27 (brs, 1H); *M/z* (-) 268 (M^-), 266, 196, 194.

Preparation 2

Ethyl 3-benzylthioindole-2-carboxylate

Potassium carbonate (3.5 g) was added to a solution of ethyl 3-bromoindole-2-carboxylate (5.4 g) and benzyl mercaptan (3.05 ml) in DMF (100 ml), and the reaction heated at 100°C for 3 hours. The reaction was then cooled, poured into water and extracted with ethyl acetate. Combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography using *iso*-hexane : 5% ethyl acetate as eluent, to give the product as a white crystalline solid (3.48 g, 56%); NMR d ($CDCl_3$) 1.42 (t, 3H), 4.05 (s, 2H), 4.40 (q, 2H), 7.10 - 7.40 (m, 8H), 7.78 (d, 1H), 9.06 (brs, 1H); *M/z* (+) 312 (MH^+), 266, 166.

Preparation 3

Ethyl 3-(ethoxycarbonylmethylthio)indole-2-carboxylate

To a solution of ethyl 3-bromoindole-2-carboxylate (1.34 g) and ethyl 2-mercaptoacetate (0.96 ml) in acetone (15 ml) was added potassium carbonate (1.38 g) and the resulting mixture was heated at reflux under argon for 18 hours. The cooled mixture was poured into water and extracted with ethyl acetate. Combined organic extracts were dried ($MgSO_4$) and concentrated to a gum which was purified by column chromatography using *iso*-

hexane : ethyl acetate (1:4) to give the desired product (331 mg, 21%) NMR d ($CDCl_3$) 1.05 (t, 3H), 1.45 (t, 3H), 3.6 (s, 2H), 4.0 (q, 2H), 4.5 (q, 2H), 7.2 - 7.4 (m, 3H), 7.9 (d, 1H), 9.2 (brs, 1H); *M/z* (+) 308.3 (MH^+).

Preparation 4

Ethyl *N*-(3,4-dichlorobenzyl)-3-(morpholinosulphinyl)indole-2-carboxylate

Thionyl chloride (5 ml) was added in one portion to a solution of ethyl *N*-(3,4-dichlorobenzyl)indole-2-carboxylate (908 mg) and the resulting mixture was stirred for 18 hours. The mixture was concentrated *in vacuo*. The resulting gum was suspended in diethyl ether (12 ml) and morpholine (2.2 ml) was added in one portion. The mixture was stirred for 3 hours. The reaction was quenched with water (10 ml) extracted with dichloromethane, dried ($MgSO_4$) and concentrated to a gum which was purified by column chromatography using *iso*-hexane : ethyl acetate (1:1) as eluent to give the desired product (907 mg, 72%); NMR d ($CDCl_3$) 1.4 (t, 3H), 3.0 - 3.1 (m, 2H), 3.3 - 3.4 (m, 2H), 3.7 - 3.8 (m, 4H), 4.4 (q, 2H), 5.7 (q, 2H), 6.8 (d, 1H), 7.1 (d, 1H), 7.25 - 7.4 (m, 4H), 8.6 (d, 1H); *M/z* (-) 480 (M^-).

Preparation 5

The procedure described in Preparation 4 above was repeated using the appropriate amine. Thus was obtained the compound described below.

Ethyl *N*-(3,4-dichlorobenzyl)-3-(1,1-dioxidothiomorpholino)sulphinylindole-2-carboxylate

52% yield; NMR d ($CDCl_3$) 1.4 (t, 3H), 3.1 - 3.3 (m, 4H), 3.7-4.0 (4H, m), 4.4 (q, 2H), 5.7 (q, 2H), 6.8 (d, 1H), 7.1 (s, 1H), 7.3 - 7.5 (m, 4H), 8.6 (d, 1H); *M/z* (-) 529.1 (M^-), 527.1.

Preparation 6

***N*-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-3-sulphinic acid**

Ethyl *N*-(3,4-dichlorobenzyl)indole-2-carboxylate (1.11 g) in thionyl chloride (4.0 ml) was stirred for 16 hours, then concentrated *in vacuo*. The residue was dissolved in THF (10 ml) and water (2 ml), and stirred for a further 2 hours. The reaction was partitioned between ether and water. Combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue triturated with ether to give the product as a white solid (0.67 g, 51%); NMR d

(CD_3SOCD_3) 1.27 (t, 3H), 4.35 (q, 2H), 5.80 (s, 2H), 6.83 (d, 1H), 7.23 (t, 1H), 7.40 (m, 2H), 7.57 (d, 1H), 7.68 (d, 1H), 8.42 (d, 1H); *M/z* (-) 412 (M^-), 410, 348, 346.

Preparation 7

***N*-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-3-sulphonyl chloride**

N-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-3-sulphinic acid (0.48 g), *N*-chlorosuccinimide (0.16 g) and triethylamine (0.16 ml) were stirred in dichloromethane for 4 hours. The reaction was then concentrated *in vacuo* and the residue purified by chromatography using *iso*-hexane : 10% ethyl acetate as eluent to give the product as a white crystalline solid (0.27 g, 52%); NMR d (CD_3SOCD_3) 1.43 (t, 3H), 4.48 (q, 2H), 5.53 (s, 2H), 6.98 (m, 1H), 7.30 - 7.50 (m, 5H), 8.22 (m, 1H); *M/z* (-) 444 (*M*-H^+), 426, 410.

Preparation 8

Ethyl 3-diazoindole-2-carboxylate

Acetic acid (77 ml) was added dropwise to a suspension of sodium nitrite (82 g) and ethyl indole-2-carboxylate (25 g) in dichloromethane (1000 ml), and stirred at ambient temperature under inert atmosphere. After 2 days, further sodium nitrite (20 g) was added, and acetic acid (19 ml) was added dropwise, and the reaction left stirring for a further day. The reaction was poured into water (300 ml), extracted with dichloromethane (2 x 200 ml), and neutralised with saturated sodium hydrogen carbonate solution (300 ml). Combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to afford the product as a yellow solid (26.96 g, 95%), NMR d (CD_3SOCD_3) 1.34 (t, 3H), 4.37 (q, 2H), 7.38 (m, 2H), 7.84 (m, 2H); *M*/z (+) 216.2 (MH^+).

Preparation 9

Ethyl 3-diazo-5-methoxyindole-2-carboxylate (precursor to compound 83, 84)

To a solution of ethyl 5-methoxyindole-2-carboxylate (8.0 g) in acetone (300 ml) was added a solution of sodium nitrite (39 g) in water (100 ml) and the reaction stirred vigorously while adding dropwise HCl (2M, 98 ml) at 20-25°C during one hour. The mixture was stirred in a stoppered flask at 20°C overnight and the resulting yellow precipitate was filtered to give the product (6.0 g, 67%); NMR d ($CDCl_3$) 1.45 (t, 3H), 3.87 (s, 3H), 4.50 (q, 2H), 6.98 (m, 2H), 7.85 (d, 1H); *M*/z (+) 246 (MH^+).

Preparation 10

***t*-Butyl 3-bromo-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate**

N,N-dimethylformamide di-*t*-butyl acetal (19.90 ml) was added dropwise to a suspension of 3-bromo-*N*-(3,4-dichlorobenzyl)indole-2-carboxylic acid (8.31 g) in toluene (150 ml), under an atmosphere of argon, and stirred at ambient temperature for 2 hours. The reaction was cooled, filtered, and washed with brine (100 ml), saturated $NaHCO_3$ (aq.) (100 ml), and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford the product as a clear oil that crystallised upon standing (7.65 g, 81%); NMR d (CD_3SOCD_3) 1.49 (s, 9H), 5.76 (s, 2H), 6.86 (m, 1H), 7.24 (t, 1H), 7.35-7.68 (m, 5H); *M*/z (+) 456 (*M*H$^+$), 400.

Preparation 11

Methyl 2-methoxycarbonyl-3-indoleacetate

Phenyl hydrazine (5.7 ml), dimethyl 2-oxoglutarate (10 g) and acetic acid (1.0 ml) in methanol (100 ml) were heated at reflux for 1 hour, then concentrated *in vacuo*. The crude hydrazone (13 g) was dissolved in saturated methanolic hydrochloric acid (350 ml) and heated to 75°C for 16 hours with continual stirring. The reaction was diluted with water (200 ml) and extracted with dichloromethane. Combined organic extracts were washed with saturated aqueous sodium hydrogencarbonate solution, water, saturated aqueous sodium chloride solution and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow crystalline solid (7.0 g); NMR d (CD_3SOCD_3) 3.59 (s, 3H), 3.83 (s, 3H), 4.12 (s, 2H), 7.06 (t, 1H), 7.26 (t, 1H), 7.41 (d, 1H), 7.63 (d, 1H), 11.76 (brs, 1H); *M*/z (-) 246 (*M*-H$^+$).

Preparation 12

Methyl *N*-(3,4-dichlorobenzyl)-2-methoxycarbonyl-3-indoleacetate

3,4-Dichlorobenzyl chloride (8.2 g) was added to a stirred solution of methyl 2-methoxycarbonyl-3-indoleacetate (6.5 g) and potassium carbonate (8.36 g) in acetonitrile (200 ml) under an atmosphere of argon. The reaction was heated to 80°C for 24 hours. The reaction was concentrated *in vacuo* and partitioned between ethyl acetate and water. Combined organic extracts were washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography using 25% ethyl acetate : *iso*-hexane as eluent to give the product as a white

solid (6.95 g, 65%); NMR d (CD_3SOCD_3) 3.60 (s, 3H), 3.77 (s, 3H), 4.13 (s, 2H), 5.89 (s, 2H), 6.89 (dd, 1H), 7.16 (t, 1H), 7.27 (d, 1H), 7.34 (t, 1H), 7.52 (d, 1H), 7.57 (d, 1H), 7.78 (d, 1H); *M/z* (+) 406 (MH^+).

Preparation 13

Methyl 3-aminoindole-2-carboxylate

To a solution of ethyl 3-aminoindole-2-carboxylate [Prepared according to P. Unangst, *J. Het. Chem.*, 1983, **20**, 495] (5.0 g) in methanol (50 ml) was added sodium methoxide (6.5 g). The resulting mixture was stirred for 4 hours and then quenched with saturated ammonium chloride solution. The resulting mixture was extracted with dichloromethane, dried ($MgSO_4$) and evaporated to give a gum which was purified by column chromatography using *iso*-hexane : ethyl acetate (1:4) as eluent to give the desired product (1.95 g, 42%); NMR d (CD_3SOCD_3), 3.8 (s, 3H), 5.7 (s, 2H), 6.8 - 6.9 (m, 1H), 7.2 (m, 2H), 7.7 (d, 1H); *M/z* (+) 191.1 (MH^+).

Preparation 14

Ethyl 3-formylindole-2-carboxylate

A mixture of *N*-methylformanilide (2.25 ml) and phosphoryl chloride (1.70 ml) was stirred at ambient temperature for 15 minutes. 1,2-dichloroethane (30 ml) was then added, followed by ethyl indole-2-carboxylate (3 g) and the reaction was heated at reflux for 90 minutes. The reaction mixture was then poured into a mixture of ice / water (200 ml) and sodium acetate (10 g) and extracted with ethyl acetate (2 x 200 ml). Combined organic phases were evaporated and the crude residue purified by column chromatography using dichloromethane as eluent to give the product as a white solid (2.27 g, 66%); NMR d (CD_3SOCD_3) 1.40 (t, 3H), 4.42 (q, 2H), 7.25 (m, 1H), 7.40 (m, 1H), 7.55 (m, 1H), 8.20 (m, 1H), 12.77 (s, 1H); *M/z* (+) 218.3 (MH^+).

Preparation 15

Ethyl 3-formyl-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate

Sodium hydride (488 mg, 60% in mineral oil) was added to a stirred solution of ethyl 3-formylindole-2-carboxylate (2.21 g) in DMF (100 ml) under argon, and reaction stirred at ambient temperature for 25 minutes. 3,4-Dichlorobenzyl chloride (1.71 ml) was then added and the reaction stirred overnight. The reaction mixture was concentrated *in vacuo* and the

residue dissolved in ethyl acetate (80 ml) and washed with water (2 x 80 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude residue which was purified by column chromatography using ethyl acetate : *iso*-hexane as eluent (gradient 5/95 - 100/0), to give the product as a yellow solid (2.17g, 57%); NMR d (CD_3SOCD_3) 1.25 (t, 3H), 4.40 (q, 2H), 5.80 (s, 2H), 7.00 (m, 1H), 7.30 - 7.50 (m, 3H), 7.55 (m, 1H), 7.65 (m, 1H), 8.35 (m, 1H), 10.48 (s, 1H) ; *M*/z (+) 376.4 (MH^+).

Preparation 16

Ethyl *N*-(3,4-dichlorobenzyl)-2-ethoxycarbonylindole-3-carboxylate

A mixture of sodium chlorite (3.39 g) and sodium dihydrogen orthophosphate (4.54 g) in water (50 ml) was added dropwise to a stirred solution of ethyl 3-formyl-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (1.56 g) and 2-methylbut-2-ene (50 ml) in *tert*-butyl alcohol (100 ml) at ambient temperature and reaction stirred vigorously overnight. The reaction mixture was concentrated *in vacuo* and the residue dissolved in dichloromethane (100 ml), washed with water (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the product as a yellow solid (1.50 g, 92%); NMR d (CD_3SOCD_3) 1.20 (t, 3H), 4.30 (q, 2H), 5.50 (s, 2H), 7.00 (m, 1H), 7.25 (m, 2H), 7.42 (m, 1H), 7.58 (m, 2H), 8.00 (m, 1H), 12.68 (s, 1H); *M*/z (-) 390.4 (M-H^+).

Example 1

Ethyl *N*-(3,4-dichlorobenzyl)-3-benzylthioindole-2-carboxylate (Ethyl ester of Compound 5)

Powdered sodium hydroxide (3.2 g) was added in a single portion to a vigorously stirred solution of ethyl 3-benzylthioindole-2-carboxylate (2.48 g), 3,4-dichlorobenzyl chloride (1.71 g) and tetra-*n*-butylammonium hydrogensulphate (0.5 g) in dichloromethane (100 ml). The reaction was stirred for 6 hours then partitioned between 2M HCl and ethyl acetate. Combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by column chromatography using *iso*-hexane : 5% ethyl acetate as eluent to give the product as a white crystalline solid (2.26 g, 60%); NMR d (CD_3SOCD_3) 1.32 (t, 3H), 4.00 (s, 2H), 4.25 (q, 2H), 5.60 (s, 2H), 6.78 (d, 1H), 7.04 (m, 2H), 7.10 - 7.38 (m, 8H), 7.80 (d, 1H); *M/z* (+) 470 (M^+), 426, 424.

Example 2

The procedure described in Example 1 above was repeated using the appropriate indole. Thus were obtained the compounds described below.

Ethyl 3-bromo-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (precursor to Compound 73)

98% yield; NMR d (CD_3SOCD_3) 1.26 (t, 3H), 4.30 (q, 2H), 5.79 (s, 2H), 6.89 (d, 1H), 7.25 (s, 1H), 7.33 - 7.46 (m, 2H), 7.50 (d, 1H), 7.57 - 7.68 (m, 2H), *M*/z (+) 430.1 (MH^+).

Ethyl *N*-(3,4-dichlorobenzyl)-3-(2,2-dimethyl-1,3-dioxolane-4-ylmethoxy)indole-2-carboxylate (Ethyl ester of Compound 70)

71% yield; NMR d (CD_3SOCD_3) 1.26 (t, 3H), 1.29 (s, 3H), 1.34 (s, 3H), 3.84 (t, 1H), 4.10 (m, 1H), 4.25 (q, 2H), 4.42 (m, 1H), 5.71 (s, 2H), 6.86 (m, 1H), 7.13 (t, 1H), 7.32 (m, 2H), 7.53 (m, 2H), 7.77 (d, 1H); *M*/z (+) 478.3 (MH^+).

Ethyl *N*-(3,4-dichlorobenzyl)-3-[2-(*N*-acetyl-*N*-phenylamino)ethoxy]indole-2-carboxylate (Ethyl ester of Compound 76)

82% yield; NMR d (CD_3SOCD_3) 1.22 (t, 3H), 3.27 (s, 3H), 3.44 (t, 2H), 4.15 (t, 2H), 4.25 (q, 2H), 5.70 (s, 2H), 6.85 (d, 1H), 7.10 (t, 1H), 7.27 (m, 7H), 7.53 (m, 2H), 7.64 (d, 2H); *M*/z (+) 525.5 (MH^+).

Ethyl *N*-(3,4-dichlorobenzyl)-3-(3-furylmethoxy)indole-2-carboxylate (Ethyl ester of Compound 77)

64% yield; NMR d (CD_3SOCD_3) 1.23 (t, 3H), 4.24 (q, 2H), 5.09 (s, 2H), 5.71 (s, 2H), (s, 1H), 6.83 (d, 1H), 7.10 (t, 1H), 7.29 (m, 2H), 7.51 (t, 2H), 7.65 (m, 3H); *M*/z (+) 444.4 (MH^+).

Ethyl *N*-(3,4-dichlorobenzyl)-3-(cyclohex-2-enylmethoxy)indole-2-carboxylate (Ethyl ester of Compound 78)

83% yield; NMR d (CD_3SOCD_3) 1.24 (t, 3H), 1.42 (m, 1H), 1.91 (m, 2H), 2.04 (m, 3H), 2.19 (m, 1H), 4.10 (m, 2H), 4.25 (q, 2H), 5.68 (s, 2H), 5.70 (s, 2H), 6.84 (d, 1H), 7.13 (t, 1H), 7.32 (m, 2H), 7.52 (m, 2H), 7.74 (d, 1H); *M*/z (+) 458.4 (MH^+).

Ethyl *N*-(3,4-dichlorobenzyl)-3-[4-(hydroxymethyl)cyclohexylmethoxy]indole-2-carboxylate (Ethyl ester of Compound 79)

69% yield; NMR d ($CDCl_3$) 0.82 - 2.15 (m, 10H), 1.36 (t, 3H), 3.50 (d, 2H), 4.07 (d, 2H), 4.35 (q, 2H), 5.64 (s, 2H), 6.81 (d, 2H), 7.12 (m, 2H), 7.27 (m, 3H), 7.75 (d, 2H); *M*/z (+) 490.5 (MH^+).

Ethyl *N*-(3,4-dichlorobenzyl)-3-(4-chlorophenethyloxy)indole-2-carboxylate (Ethyl ester of Compound 80)

87% yield; NMR d (CD_3SOCD_3) 1.21 (t, 3H), 3.07 (t, 2H), 4.21 (q, 2H), 4.37 (t, 2H), 5.70 (s, 2H), 6.84 (d, 1H), 7.07 (t, 1H), 7.31 (m, 6H), 7.51 (t, 3H); *M*/z (+) 504.5 (MH^+).

Compound 23 ethyl ester

29% yield; NMR d ($CDCl_3$) 1.35 (t, 3H), 3.4 (t, 1H), 3.9 - 4.0 (m, 2H), 4.3 - 4.5 (m, 4H), 5.6 (s, 2H), 6.8 (d, 1H), 7.1 - 7.4 (m, 5H), 7.8 (d, 1H); *M/z* (+) 410.3 (MH^+), 408.2.

Compound 26 ethyl ester

45% yield; NMR d ($CDCl_3$) 1.35 (t, 3H), 3.2 (t, 2H), 4.3 (q, 2H), 4.45 (t, 2H), 5.65 (s, 2H), 6.8 (dd, 1H), 7.05 - 7.4 (m, 10H), 7.5 (d, 1H); *M/z* (+) 470.3 (MH^+), 468.4.

2-ethyl ester & methyl ester of Compound 27

66% yield; *M/z* (+) 438.3 (MH^+), 436.2.

Ethyl ester of Compound 66

62% yield; NMR d ($CDCl_3$) 1.4 (t, 3H), 3.5 (s, 3H), 4.3 - 4.4 (m, 4H), 5.65 (s, 2H), 6.85 (dd, 1H), 7.1 - 7.4 (m, 5H), 7.8 (d, 1H); *M/z* (+) 424 (MH^+), 422.

Ethyl ester of Compound 67

73% yield; NMR d ($CDCl_3$) 1.4 (t, 3H), 1.5 (s, 9H), 3.7 (q, 2H), 4.4 (q, 2H), 5.65 (s, 2H), 6.8 (dd, 1H), 7.1 - 7.4 (m, 5H), 7.9 (d, 1H); *M/z* (+) 507.3 (MH^+).

Methyl 3-amino-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (Precursor to Compound1, 2)

64% yield; NMR d (CD_3SOCD_3) 3.75 (s, 3H), 5.6 (s, 2H), 6.0 (s, 2H), 6.8 - 7.0 (m, 2H), 7.1 - 7.5 (m, 4H), 7.85 (d, 1H); *M/z* (+) 351.2 (*M*H$^+$), 349.2.

Di-ethyl ester Compound 24

38% yield; NMR d ($CDCl_3$) 1.05 (t, 3H), 1.4 (t, 3H), 3.6 (s, 2H), 3.95 (q, 2H), 4.4 (q, 2H), 5.7 (s, 2H), 6.85 (dd, 1H), 7.2 - 7.4 (m, 5H), 7.9 (d, 1H); *M/z* (+) 468.3 (*M*H$^+$), 466.3.

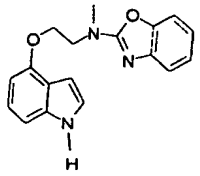
Ethyl 3-amino-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (Precursor to Compound 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22)

44% yield; NMR d (CD_3SOCD_3) 1.21 (t, 3H), 4.21 (q, 2H), 5.56 (s, 2H), 6.00 (s, 2H), 6.86 (d, 1H), 6.98 (t, 1H), 7.22 (d, 1H), 7.30 (t, 1H), 7.40 (d, 1H), 7.48 (d, 1H), 7.86 (d, 1H); *M/z* (+) 363 (*M*H$^+$).

Example 3

Ethyl ester of Compound 73

Sodium hydride (23 mg, 60% dispersion in mineral oil) was added in a single portion to a stirred solution of compound of formula (A) (0.19 g) in DMF (3.0 ml) and the reaction stirred for 30 mins.



(A)

3,4-Dichlorobenzyl chloride (0.1 ml) was added and the reaction stirred for 16 hours. The reaction was poured into water and extracted with ethyl acetate. Combined organic extracts were dried ($MgSO_4$) and concentrated and the residue purified by chromatography using *iso*-hexane : 20% ethyl acetate as eluent to give the product as a colourless oil (0.23 g, 85%); *M/z* (+) 540, 538 (*M*H$^+$).

Example 4

The procedure described in Example 3 above was repeated using the appropriate indole. Thus were obtained the compounds described below.

Ethyl ester of Compound 74

93% yield; *M/z* (+) 545, 543 (MH^+).

Ethyl ester of Compound 75

73% yield; *M/z* (+) 507, 505 (MH^+), 461, 459, 318.

Ethyl *N*-(3,4-dichlorobenzyl)indole-2-carboxylate

60% yield; *M/z* (+) 349 (MH^+)

Diethyl *N*-(3,4-dichlorobenzyl)-2,3-dicarboxylate

74% yield; *M/z* (+) 392, 394 (MH^+)

Example 5

Ethyl *N*-(3,4-dichlorobenzyl)-3-(2-ethoxyethoxy)-5-methoxyindole-2-carboxylate (Ethyl ester of Compound 82)

To a solution of ethyl *N*-(3,4-dichlorobenzyl)-3-(2-ethoxyethoxy)-5-methoxyindole-2-carboxylate (3.0 g) in DMF (50 ml) was add anhydrous potassium carbonate (3.0 g), 3.4-dichlorobenzyl chloride (2.0 ml) and potassium iodide (100 mg), and the reaction stirred at 60°C for 3 hours. The solvent was evaporated *in vacuo* and the residue partitioned between water (200 ml) and ether (200 ml), the organic layer was dried ($MgSO_4$) and evaporated to give a gum, which was purified by column chromatography using *iso*-hexane : ethyl acetate (4:1) to give the product (2.5 g, 55%); NMR d ($CDCl_3$) 1.25 (t, 3H), 1.38 (t, 3H), 3.62 (q, 2H), 3.80 (t, 2H), 3.86 (s, 3H), 4.3 - 4.4 (m, 4H), 5.62 (s, 2H), 6.80 (dd, 1H), 6.96 (dd, 1H), 7.12 (s, 1H), 7.14 (d, 1H), 7.20 (d, 1H), 7.26 (d, 1H).

Example 6

The procedure described in Example 5 above was repeated using the appropriate indole and benzyl halide. Thus was obtained the compound described below.

Ethyl *N*-(3,4-dichlorobenzyl)-3-(2-hydroxyethoxy)-5-methoxyindole-2-carboxylate (Ethyl ester of Compound 83)

38% yield; NMR d ($CDCl_3$) 1.32 (t, 3H), 3.42 (t, 1H), 3.87 (s, 3H), 3.92 (m, 2H), 4.3 - 4.4 (m, 4H), 5.60 (s, 2H), 6.80 (dd, 1H), 7.02 (dd, 1H), 7.1 - 7.2 (m, 3H), 7.32 (d, 1H); *M/z* (+) 440 (*M*H$^+$), 438.

Example 7

***N*-(3,4-Dichlorobenzyl)-3-benzylsulphinylindole-2-carboxylic acid (Compound 25)**

A solution of ethyl *N*-(3,4-dichlorobenzyl)-3-benzylthioindole-2-carboxylate (0.50 g) in dichloromethane (2 ml) was added to a slurry of wet alumina (1 g) and Oxone® (0.615 g) in dichloromethane (10 ml). The mixture was then heated at reflux for two hours, and allowed to cool. The product was washed away from the alumina using methylene chloride (200 ml). The solution was then dried ($MgSO_4$) and evaporated to afford the crude sulphoxide ester (103 mg). The crude ester was dissolved in THF (2 ml) and methanol (1 ml), and sodium hydroxide (2M, 3 ml) was added. The solution was stirred for five hours, then concentrated *in vacuo*. The residue was dissolved in water (10 ml) and the product precipitated by dropwise addition of aqueous HCl (2M, 10 ml). The resulting solid was collected by filtration and washed with cold water, then dried *in vacuo* to afford the product as a pale yellow solid (36 mg, 7 %, 2 steps), NMR d (CD_3SOCD_3) 4.37 (d, 2H), 5.83 (d, 2H), 6.96 (dd, 1H), 7.10 (m, 3H), 7.20 (m, 3H), 7.30 (t, 1H), 7.38 (d, 1H), 7.59 (s, 1H), 7.62 (s, 1H), 8.05 (d, 1H); *M/z* (-) 456 (*M*-H$^-$), 412, 365, 323, 323, 321, 320.

Example 8

Ethyl *N*-(3,4-dichlorobenzyl)-3-benzylsulphonylindole-2-carboxylate (Ethyl ester of Compound 21)

To a solution of ethyl *N*-(3,4-dichlorobenzyl)-3-benzylthioindole-2-carboxylate (520 mg) in acetic acid (12 ml) was added hydrogen peroxide solution (30%, 2.5 ml) and the resulting mixture was stirred for 18 hours. The reaction mixture was poured into water (20 ml), made basic with sodium bicarbonate and extracted with dichloromethane. The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography using *iso*-hexane : 20% ethyl acetate as eluent to give the product as a yellow gum (205 mg, 37%); NMR d ($CDCl_3$) 1.4 (t, 3H), 4.45 (q, 2H), 4.6 (s, 2H), 5.5 (s, 2H), 6.9 (dd, 1H), 7.1 - 7.3 (m, 9H), 7.4 (d, 1H), 7.7 (d, 1H); *M/z* (+) 504.3 (*M*H$^+$), 502.4.

Example 9

The procedure described in Example 8 above was repeated using the appropriate thioindole. Thus was obtained the compound described below.

Di-ethyl ester of Compound 51

48% yield; *M/z* (+) 500.2 (MH^+), 498.3.

Example 10

***N*-(3,4-Dichlorobenzyl)-3-benzylthioindole-2-carboxylic acid (Compound 5)**

Ethyl *N*-(3,4-dichlorobenzyl)-3-benzylthioindole-2-carboxylate (0.31 g) was dissolved in THF / methanol (1:1) and sodium hydroxide (2M, 2.0 ml) was added and the reaction stirred for 16 hours. The reaction was then concentrated *in vacuo* and the residue dissolved in water. The solution was acidified by dropwise addition of acetic acid, resulting in the precipitation of a white solid which was filtered, washed with water and dried *in vacuo* to give the desired end product (0.082 g, 28%); NMR d (CD_3SOCD_3) 4.04 (s, 2H), 5.72 (s, 2H), 6.83 - 7.62 (m, 12H); *M/z* (-) 442 (M^+), 440, 428, 398, 396, 307, 305.

Example 11

The procedure described in Example 10 above was repeated using the appropriate ester. Thus were obtained the compounds described below.

Compound 70

70% yield; NMR d (CD_3SOCD_3) 1.30 (s, 3H), 1.35 (s, 3H), 3.87 (m, 1H), 4.10 (m, 3H), 4.40 (m, 1H), 5.75 (s, 2H), 6.90 (d, 2H), 7.13 (t, 1H), 7.32 (m, 2H), 7.51 (m, 2H), 7.75 (d, 2H); *M*/z (-) 448.2 (M-H^+).

Compound 76

85% yield; NMR d (CD_3SOCD_3) 3.35 (m, 2H), 3.44 (s, 3H), 5.80 (s, 2H), 7.10 (m, 2H), 7.21 (m, 6H), 7.42 (m, 3H), 7.59 (d, 1H); *M*/z (-) 495.4 (M-H^+).

Compound 77

61% yield; NMR d (CD_3SOCD_3) 5.10 (s, 2H), 5.77 (s, 2H), 6.58 (s, 1H), 6.89 (d, 1H), 7.07 (t, 1H), 7.27 (m, 2H), 7.50 (m, 2H), 7.62 (m, 3H); *M*/z (-) 414.2 (*M*-H^+).

Compound 78

57% yield; NMR d (CD_3SOCD_3) 1.40 (m, 1H), 2.00 (m, 6H), 4.08 (d, 2H), 5.67 (s, 2H), 5.73 (s, 2H), 6.90 (m, 1H), 7.10 (m, 1H), 7.30 (m, 2H), 7.52 (m, 2H), 7.70 (m, 1H); *M*/z (-) 428.3 (*M*-H^+).

Compound 79

68% yield; NMR d (CD_3SOCD_3) 0.96 (m, 4H), 1.52 (m, 1H), 1.77 (m, 2H), 1.90 (m, 3H), 3.20 (d, 2H), 3.96 (d, 2H), 5.78 (s, 2H), 7.00 (m, 2H), 7.15 (t, 1H), 7.35 (m, 2H), 7.50 (m, 2H); *M*/z (-) 460.4 (*M*-H^+).

Compound 80

65% yield; NMR d (CD_3SOCD_3) 2.99 (t, 2H), 4.35 (t, 2H), 5.80 (s, 2H), 6.87 (t, 1H), 7.04 (m, 2H), 7.23 (m, 2H), 7.36 (m, 5H), 7.48 (d, 1H); *M*/z (-) 474.3 (*M*-H^+).

Compound 71

91% yield; NMR d (CD_3SOCD_3) 3.52 (m, 2H), 3.86 (m, 1H), 4.12 (m, 1H), 4.27 (m, 1H), 5.74 (s, 2H), 6.90 (d, 1H), 7.18 (t, 1H), 7.38 (m, 2H), 7.58 (m, 2H), 7.87 (d, 1H), *M*/z (-) 408.2 (*M*-H^+).

3-Bromo-*N*-(3,4-dichlorobenzyl)indole-2-carboxylic acid (precursor to Compound 72)

90% yield; NMR d (CD_3SOCD_3) 5.83 (s, 2H), 6.89 (m, 1H), 7.25 (t, 1H), 7.39 (m, 2H), 7.51 (d, 1H), 7.60 (m, 2H); *M*/z (-) 398.2 (*M*-H^+), 354.3.

Compound 73

48% yield; *M/z* (-) 510 (*M*$^-$), 508, 466, 464.

Compound 74

21% yield; *M/z* (-) 515 (*M*$^-$), 513, 425, 143.

Compound 75

53% yield; *M/z* (-) 477 (M^+), 475, 431, 290.

***N*-(3,4-Dichlorobenzyl)-2-carboxylic acid-3-indoleacetic acid (Compound 28)**

92% yield; NMR d (CD_3SOCD_3) 3.72 (s, 2H), 5.80 (s, 2H), 7.00 - 7.10 (m, 2H), 7.16 (t, 1H), 7.33 - 7.40 (m, 2H), 7.49 (d, 1H), 7.58 (d, 1H); *M/*z (-) 376 (*M*-H^+).

Compound 68

57% yield; NMR d (CD_3SOCD_3) 1.50 - 2.00 (m, 4H), 3.60 (q, 1H), 3.80 (q, 1H), 3.90 (m, 1H), 5.75 (s, 2H), 7.10 (m, 3H), 7.35 (d, 1H), 7.45 (s, 1H), 7.50 (d, 1H), 8.25 (d, 1H); *M/*z (-) 445.2 (*M*-H^+).

Compound 81

93% yield; NMR d (CD_3SOCD_3) 2.25 (m, 1H), 3.05 - 3.60 (m, 5H), 4.80 (m, 1H), 5.90 (s, 2H), 7.05 (m, 1H), 7.30 (t, 1H), 7.40 (m, 2H), 7.65 (m, 2H), 7.80 (m, 1H), 8.95 (m, 1H); *M/*z (-) 479.4 (*M*-H^+).

Compound 84

58% yield; *M/*z(-) 479.2 (*M*-H^+).

Compound 85

81% yield; *M/*z (-) 470.2 (*M*-H^+).

***(Z)*-*N*-(3,4-Dichlorobenzyl)-2-carboxyindole-3-acrylic acid (Compound 50)**

81% yield; NMR d (CD_3SOCD_3) 5.80 (s, 2H), 6.50 (d, 1H), 6.90 (m, 1H), 7.30 (m, 3H), 7.50 (d, 1H), 7.60 (m, 1H), 8.00 (m, 1H), 8.40 (d, 1H); *M/*z (-) 388.4 (*M*-H^+).

***N*-(3,4-Dichlorobenzyl)-3-(2-ethoxyethoxy)-5-methoxyindole-2-carboxylic acid (Compound 82)**

60% yield; NMR d (CD_3SOCD_3) 1.14 (t, 3H), 3.46 (q, 2H), 3.60 (t, 2H), 3.73 (s, 3H), 4.25 (t, 2H), 5.80 (s, 2H), 6.70 (dd, 1H), 6.95 (d, 1H), 7.1 - 7.2 (m, 2H), 7.32 (d, 1H), 7.46 (d, 1H); *M*/z (-) 438 (*M*-H^+), 438.

Compound 23

84% yield; NMR d (CD_3SOCD_3) 3.7 (t, 2H), 4.2 (t, 2H), 5.7 (s, 2H), 6.9 (dd, 1H), 7.1 (t, 1H), 7.3 - 7.4 (m, 2H), 7.5 - 7.6 (m, 2H), 7.8 (d, 1H); *M/z* (-) 380.2 (M^-), 378.2.

Compound 26

87% yield; NMR d (CD_3SOCD_3) 3.1 (t, 2H), 4.35 (t, 2H), 5.7 (s, 2H), 6.9 (dd, 1H), 7.05 (t, 1H), 7.2 - 7.4 (m, 7H), 7.45 - 7.76 (m, 4H); *M/z* (-) 440.2 (M^-), 438.1.

Compound 27

94% yield; NMR d (CD_3SOCD_3) 4.6 (s, 2H), 5.7 (s, 2H), 6.95 (dd, 1H), 7.1 (t, 1H), 7.2 (t, 1H), 7.37 (d, 1H), 7.4 - 7.5 (m, 2H), 7.7 (d, 1H); *M/z* (-) 394 (M^-), 392.

Compound 66

49% yield; NMR d (CD_3SOCD_3) 3.6 (t, 2H), 4.25 (t, 2H), 5.85 (s, 2H), 6.9 (t, 1H), 7.0 (t, 1H), 7.1 (dd, 1H), 7.25 (d, 1H), 7.4 (s, 1H), 7.5 (d, 2H); *M/z* (-) 394.2 (M^-), 392.1.

Compound 67

59% yield; NMR d (CD_3SOCD_3) 1.4 (s, 9H), 3.3 (s, 3H), 4.1 (t, 2H), 5.7 (s, 2H), 6.8 - 7.0 (m, 2H), 7.1 (d, 1H), 7.3 - 7.4 (m, 2H), 7.5 (t, 2H), 7.7 (d, 1H); *M/z* (-) 479.3 (M^+).

Compound 1

84% yield; NMR d (CD_3SOCD_3) 5.9 (s, 2H), 6.95 (dd, 1H), 7.1 (t, 1H), 7.3 - 7.4 (m, 2H), 7.5 - 7.7 (m, 4H), 7.8 (d, 1H), 8.0 (d, 1H), 8.1 (s, 1H); *M/z* (-) 473.1 (M^-), 471.1.

Compound 2

47% yield; NMR d (CD_3SOCD_3) 5.85 (s, 2H), 6.95 (d, 1H), 7.1 (t, 1H), 7.3 - 7.4 (m, 2H), 7.5 (d, 1H), 7.8 (d, 1H); *M/z* (-) 413.1 (M^-), 411.1.

***N*-(3,4-Dichlorobenzyl)-3-benzylsulphonylindole-2-carboxylic acid (Compound 21)**

81% yield; NMR d (CD_3SOCD_3) 4.8 (s, 2H), 5.7 (s, 2H), 7.0 - 7.25 (m, 8H), 7.4 - 7.6 (m, 4H); *M/z* (+) 474.3 (MH^+).

Compound 24

98% yield; NMR d (CD_3SOCD_3) 3.6 (s, 2H), 5.75 (s, 2H), 6.9 (dd, 1H), 7.2 - 7.4 (m, 3H), 7.5 (dd, 2H), 7.8 (d, 1H); *M/z* (-) 410.1 (M^-), 408.1.

***N*-(3,4-Dichlorobenzyl)-3-(2-hydroxyethoxy)-5-methoxyindole-2-carboxylic acid (Compound 83)**

93% yield; NMR d (CD_3SOCD_3) 3.46 (t, 2H), 3.74 (s, 3H), 4.14 (t, 2H), 5.80 (s, 2H), 6.63 (dd, 1H), 7.96 (d, 1H), 7.06 (dd, 1H), 7.20 (d, 1H), 7.30 (s, 1H), 7.46 (d, 1H); *M/z* (-) 410 ($M-H^+$), 408.

***N*-(3,4-Dichlorobenzyl)-3-morpholinosulphonylindole-2-carboxylic acid (Compound 3)**

59% yield; NMR d ($CDCl_3$) 3.05 - 3.15 (m, 4H), 3.7 - 3.8 (m, 4H), 5.7 (s, 2H), 6.9 (dd, 1H), 7.2 - 7.5 (m, 5H), 8.2 (d, 1H); *M/z* (+) 471 (MH^+), 469.

***N*-(3,4-Dichlorobenzyl)-3-(1,1-dioxidothiomorpholino)sulphonylindole-2-carboxylic acid (Compound 4)**

93% yield; NMR d (CD_3SOCD_3), 3.1 - 3.2 (m, 4H), 3.7 - 3.8 (m, 4H), 5.45 (s, 2H), 7.1 - 7.2 (m, 2H), 7.3 - 7.45 (m, 2H), 7.5 (d, 1H), 7.7 - 7.8 (m, 2H); *M/z* (+) 519.2 (MH^+), 517.2.

Compound 51

23% yield; NMR d (CD_3SOCD_3), 4.1 (s, 2H), 5.6 (s, 2H), 7.1 (m, 2H), 7.3 - 7.4 (m, 2H), 7.5 (d, 1H), 7.7 (s, 1H), 7.9 (m, 1H); *M/z* (-) 442 (M^-), 440.

Compound 86

27% yield; NMR d (CD_3SOCD_3) 6.65 (s, 2H),7.45 (dd, 1H), 7.6-7.75 (m, 2H), 7.8 (d, 1H), 7.95 (t, 1H), 8.95 (d, 1H); *Mz* (-) 362, 364 (M^+)

Example 12

Ethyl *N*-(3,4-dichlorobenzyl)-3-morpholinosulphonylindole-2-carboxylate [Ethyl ester of Compound 3]

To a suspension of ethyl *N*-(3,4-dichlorobenzyl)-3-morpholinosulphinylindole-2-carboxylate (803 mg) in acetone (40 ml) was added a solution of potassium permanganate (528 mg) in water (15 ml). The resulting mixture was stirred for 18 hours. The mixture was poured into water (20 ml) and extracted with diethyl ether, dried ($MgSO_4$) and concentrated to a gum which was purified by column chromatography using *iso*-hexane : ethyl acetate (3:1) as eluent to give the desired product (681 mg, 82%); NMR d ($CDCl_3$) 1.3 (t, 3H), 3.2 - 3.2 (m, 4H), 3.7 - 3.8 (m, 4H), 5.4 (s, 2H), 6.95 (d, 1H), 7.3 - 7.4 (m, 5H), 8.05 (d, 1H); *M/z* (+) 499.2 (MH^+), 497.3.

Example 13

The procedure described above in Example 12 was repeated using the appropriate amine. Thus was obtained the compound described below.

Ethyl *N*-(3,4-dichlorobenzyl)-3-(1,1-dioxidothiomorpholino)sulphonylindole-2-carboxylate [Ethyl ester Compound 4]

49% yield; NMR d ($CDCl_3$) 1.3 (t, 3H), 3.1 - 3.2 (m, 4H), 3.9 - 4.0 (m, 4H), 4.4 (q, 2H), 5.4 (s, 2H), 6.9 (dd, 1H), 7.2 - 7.4 (m, 5H), 8.0 (d, 1H); *M/z* (-) 545.2 (M^-), 543.1.

Example 14

Compound 6

N-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-3-sulphonyl chloride (0.12 g), *N*-methylpiperazine (0.15 ml), triethylamine (0.19 ml) and 4-dimethylaminopyridine (30 mg) were stirred for 4 hours in dichloromethane (2.0 ml). The reaction was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF / methanol (1:1) and sodium hydroxide (3M, 1.0 ml) was added and the reaction stirred for 16 hours. The reaction was then concentrated *in vacuo* and the residue dissolved in water. The solution was acidified by dropwise addition of acetic acid, resulting in the precipitation of a white solid which was filtered, washed with water and dried *in vacuo* to give the desired end product (61 mg, 47%, 2 steps); NMR d (CD_3SOCD_3) 2.57 (s, 3H), 3.00 (m, 4H), 3.32 (m, 4H), 5.37 (s,

2H), 7.19 (m, 2H), 7.28 (d, 1H), 7.43 (m, 2H), 7.65 (s, 1H), 7.80 (m, 1H); *M/z* (+) 482 (M^+), 236, 215, 196, 159, 142.

Example 15

The procedure described in Example 14 above was repeated using the appropriate amines. Thus were obtained the compounds described below.

Compound 7

57% yield (2 steps); NMR d (CD_3SOCD_3) 2.63 (s, 6H), 3.10 (m, 4H), 5.68 (s, 2H), 7.12 - 7.26 (m, 3H), 7.44 - 7.60 (m, 3H), 7.96 (m, 1H), 8.37 (t, 1H); *M/z* (+) 470 (M^+), 214, 158, 141, 123.

Compound 29

61% yield (2 steps); *M/z* (-) 457 (M^+), 455, 413, 411.

Compound 30

30% yield (2 steps); *M/z* (-) 487 (M^+), 485, 443, 441, 399, 397, 355, 353.

Compound 31

23% yield (2 steps); *M/z* (-) 492 (M-H^+), 449, 420, 400, 398, 354, 308, 222.

Compound 32

45% yield (2 steps); *M/z* (-) 497 (M^+), 495, 453, 451.

Compound 33

44% yield (2 steps); *M/z* (-) 436 (M-CO_2^+), 434.

Compound 34

40% yield (2 steps); *M/z* (-) 493 (M^+), 449, 447, 340, 338.

Compound 35

49% yield (2 steps); *M/z* (-) 512 (M^+), 510, 468, 466.

Compound 36

60% yield (2 steps); *M/z* (-) 512 (M^+), 510, 468, 466.

Compound 37

52% yield (2 steps); *M/z* (-) 446 (M-CO_2^+), 444.

Compound 38

43% yield (2 steps); *M/z* (-) 443 (M-CO_2^+), 441.

Compound 39

29% yield (2 steps); *M/z* (-) 393 (M-CO_2^+), 391.

Compound 40

54% yield (2 steps); *M/z* (-) 515 (M^+), 513, 471, 469.

Compound 41

34% yield (2 steps); *M/z* (-) 465 (M-CO_2^+), 463.

Compound 42

20% yield (2 steps); *M/z* (-) 473 (M-CO_2^+), 369, 367.

Compound 43

37% yield (2 steps); *M/z* (-) 425 (M-CO_2^+), 423.

Compound 44

5% yield (2 steps); *M/z* (-) 529 (M^+), 527, 485, 483, 355, 353, 274.

Compound 45

17% yield (2 steps); *M/z* (-) 4663 (M^+), 464, 422, 420.

Compound 46

6% yield (2 steps); *M/z* (-) 451 (M-CO_2^+), 449, 409, 355, 296, 221.

Compound 47

22% yield (2 steps); *M/z* (-) 549 (M^+), 547, 505, 503, 458, 381, 379, 355, 353.

Example 16

Ethyl 3-(2,2-dimethyl-1,3-dioxolane-4-ylmethoxy)indole-2-carboxylate (Precursor to Compounds 70 and 71)

Rhodium acetate dimer (30 mg) was added to a solution of solketal (0.87 ml) and ethyl 3-diazoindole-2-carboxylate (300 mg) in dichloroethane (10 ml), and stirred at 85°C for 3 hours. The reaction was concentrated *in vacuo* and the residue purified by column chromatography using a gradient of 0% to 20% ethyl acetate : *iso*-hexane as eluent to afford the product as a pale yellow solid (435 mg, 97%); NMR d (CD_3SOCD_3) 1.27 - 1.38 (m, 9H), 3.88 (m, 1H), 4.11 (m, 3H), 4.30 (q, 2H), (m, 1H), 7.01 (t, 1H), 7.24 (t, 1H), 7.36 (d, 1H), 7.65 (d, 1H), 11.27 (s, 1H); *M*/z (+) 320.3 (MH^+).

Example 17

The procedure described in Example 16 above was repeated using the appropriate diazoindole and alcohols. Thus were obtained the compounds described below.

Ethyl 3-[2-(*N*-acetyl-*N*-phenylamino)ethoxy]indole-2-carboxylate (Precursor to Compound 76)

75% yield; NMR d (CD_3SOCD_3) 1.32 (t, 3H), 3.41 (m, 5H), 4.12 (t, 2H), 4.31 (q, 2H), 6.99 (t, 1H), 7.23 (m, 6H), 7.36 (d, 1H), 7.58 (d, 1H), 11.28 (s, 1H); *M*/z (+) 367.4 (MH^+).

Ethyl 3-(3-furylmethoxy)indole-2-carboxylate (Precursor to Compound 77)

47% yield; NMR d (CD_3SOCD_3) 1.31 (t, 3H), 4.31 (q, 2H), 5.07 (s, 2H), 6.57 (s, 1H), 6.99 (t, 1H), 7.21 (t, 1H), 7.36 (d, 1H), 7.60 (m, 3H); *M*/z (+) 286.3 (MH^+).

Ethyl 3-(cyclohex-2-enylmethoxy)indole-2-carboxylate (Precursor to Compound 78)

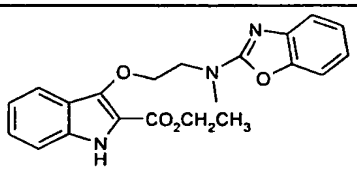
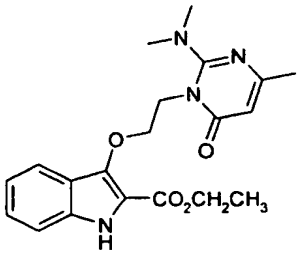
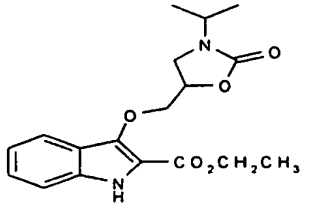
90% yield; NMR d (CD_3SOCD_3) 1.31 (t, 3H), 1.39 (m, 1H), 1.80 - 2.30 (m, 6H), 4.08 (m, 2H), 4.30 (q, 2H), 5.66 s, 2H), 7.01 (t, 1H), 7.22 (t, 1H), 7.35 (d, 1H), 7.62 (d, 1H), 11.19 (s, 1H); *M*/z (+) 300.3 (MH^+).

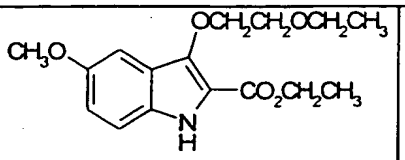
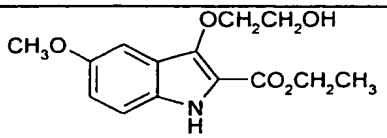
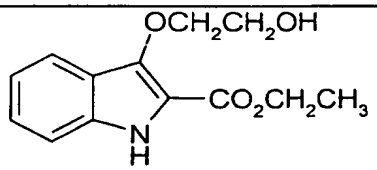
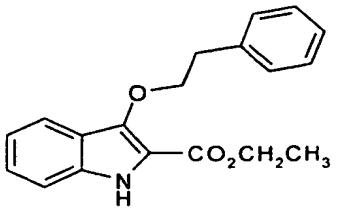
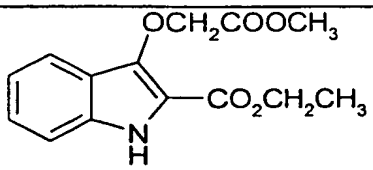
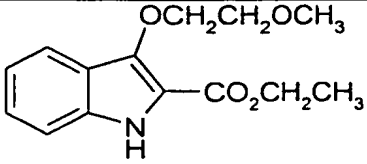
Ethyl 3-[4-(hydroxymethyl)cyclohexylmethoxy]indole-2-carboxylate (Precursor to Compound 79)

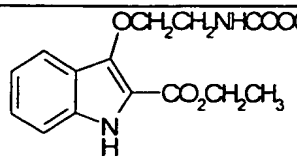
72% yield; NMR d (CD_3SOCD_3) 0.80 - 2.00 (m, 10H), 1.32 (t, 3H), 3.21 (m, 2H), 4.00 (d, 2H), 4.30 (q, 2H), 7.00 (t, 1H), 7.22 (t, 1H), 7.35 (d, 1H), 7.61 (d, 1H), 11.18 (s, 1H); *M*/z (+) 332.4 (MH^+).

Ethyl 3-(4-chlorophenethyloxy)indole-2-carboxylate (Precursor to Compound 80)

81% yield; NMR d (CD_3SOCD_3) 1.30 (t, 3H), 3.03 (t, 2H), 4.27 (q, 2H), 4.36 (t, 2H), 6.97 (t, 1H), 7.15 - 7.45 (m, 7H), 11.22 (s, 1H); *M*/z (+) 344.3 (MH^+).

Precursor to Compd No	Structure	Yield/Properties
73		47% yield; *M/z* (+) 380 (MH^+).
74		45% yield; *M/z* (+) 385 (MH^+).
75		53% yield; *M/z* (+) 347 (MH^+), 301.

82		95% yield; NMR d ($CDCl_3$) 1.24 (t, 3H), 1.42 (t, 3H), 3.60 (q, 2H), 3.80 (t, 2H), 3.85 (s, 3H), 4.38 (t, 2H), 4.42 (q, 2H), 6.96 (dd, 1H), 7.12 (d, 1H), 7.20 (d, 1H), 8.65 (s, 1H); *M*/z (+) 308 (MH^+)
83		65% yield; NMR d (CD_3SOCD_3) 1.33 (t, 3H), 3.70 (q, 2H), 3.78 (s, 3H), 4.15 (t, 2H), 4.32 (q, 2H), 4.76 (t, 1H), 6.90 (dd, 1H), 7.08 (d, 1H), 7.26 (d, 1H); *M*/z (+) 280 (MH^+).
23		80% yield; NMR d ($CDCl_3$) 1.4 (t, 3H), 3.65 (t, 1H), 3.8 - 3.9 (m, 2H), 4.4 - 4.5 (m, 4H), 7.05 - 7.1 (m, 1H), 7.35 (d, 2H), 7.7 (d, 1H), 8.3 (brs, 1H); *M*/z (+) 250.3 (MH^+).
26		92% yield; NMR d ($CDCl_3$) 1.4 (t, 3H), 3.1 (t, 1H), 4.4 (q, 2H), 4.45 (t, 2H), 7.0 - 7.1 (m, 1H), 7.2 - 7.3 (m, 7H), 7.5 (d, 1H), 8.35 (bs, 1H); *M/z* (+) 310.3 (MH^+).
27		58% yield; NMR d ($CDCl_3$) 1.4 (t, 3H), 3.8 (s, 3H), 4.4 (q, 2H), 4.9 (s, 2H), 7.1 - 7.15 (m, 1H), 7.3 - 7.4 (m, 2H), 7.8 (d, 1H), 8.4 (brs, 1H); *M/z* (+) 278.3 (MH^+).
66		94% yield; NMR d ($CDCl_3$) 1.4 (t, 3H), 3.5 (s, 3H), 3.75 (t, 2H), 4.4 - 4.5 (m, 4H), 7.1 - 7.2 (m, 2H), 7.3 (d, 2H), 7.8 (d, 1H), 8.4 (brs, 1H); *M/z* (+) 264.4 (MH^+).

67		70% yield; NMR d ($CDCl_3$) 1.4 - 1.5 (m, 12H), 3.5 - 3.6 (m, 2H), 4.35 (t, 2H), 4.5 (q, 2H), 5.65 (brs, 1H), 7.1 - 7.2 (m, 1H), 7.5 - 7.55 (m, 2H), 7.7 (d, 1H), 8.4 (brs, 1H); *M/z* (+) 349.4 (MH^+).

Example 18

Compound 69

To a suspension of ethyl *N*-(3,4-dichlorobenzyl)-3-[2-(*t*-butyloxycarbonylamino)-ethoxy]indole-2-carboxylate (112 mg) in ethyl acetate (5 ml) was added a saturated solution of HCl in dioxane (2 ml). The mixture was stirred for 18 hours and the resulting solid filtered and dried *in vacuo* (26 mg, 50%); NMR d (CD_3SOCD_3) 2.4 - 2.5 (m, 2H), 4.3 - 4.4 (m, 2H), 6.9 (d, 1H), 7.1 - 7.6 (m, 4H), 7.8 (d, 1H), 8.1 (brs, 2H); *M/z* (-) 379 (M^+), 377.

Example 19

Ethyl *N*-(3,4-dichlorobenzyl)-3-(2,3-dihydroxypropoxy)indole-2-carboxylate (Ethyl ester of Compound 71)

Ethyl *N*-(3,4-dichlorobenzyl)-3-(2,2-dimethyl-1,3-dioxolane-4-ylmethoxy)-indole-2-carboxylate [Compound 70] (15.92 g) was dissolved in tetrahydrofuran (70 ml) and hydrochloric acid (4M, 33 ml), and stirred at ambient temperature for 4 hours. The reaction was concentrated *in vacuo*, added to water (200 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*, and the residue purified by column chromatography using 70% ethyl acetate : *iso*-hexane as eluent, to afford the product as a dark yellow oil that crystallised upon standing to off white crystals (9.37 g, 65%); NMR d (CD_3SOCD_3)1.27 (t, 3H), 3.50 (m, 2H), 3.83 (m, 1H), 4.08 (m, 1H), 4.20 (m, 1H), 4.27 (q, 2H), 4.58 (t, 1H), 4.88 (d, 1H), 5.73 (s, 2H), 6.88 (d, 1H), 7.15 (t, 1H), 7.33 (m, 2H), 7.54 (m, 2H), 7.82 (d, 1H), *M/z* (+) 438.3 (MH^+).

Example 20

***t*-Butyl *N*-(3,4-dichlorobenzyl)-3-morpholinoindole-2-carboxylate (t-butyl ester of Compound 72)**

$Pd_2(dba)_3$ (114 mg), *R*-BINAP (69 mg), potassium *t*-butoxide (294 mg), and morpholine (0.209 ml) were added to a solution of *t*-butyl 3-bromo-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (1 g) in de-gassed toluene (6 ml), under an atmosphere of argon. The reaction was stirred and heated at 90°C for 16 hours then poured into water (50 ml), extracted with ethyl acetate (3 x 50 ml), and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography using 10% ethyl acetate : *iso*-hexane as eluent, to afford the product as a yellow oil (325 mg, 33%); NMR d (CD_3SOCD_3) 3.20 (t, 4H), 3.73 (t, 4H), 5.56 (s, 2H), 6.88 (d, 1H), 7.7 (t, 1H), 7.25 (m, 2H), 7.50 (m, 2H), 7.80 (d, 1H), *M*/z (+) 461 (MH^+), 405.

Example 21

***N*-(3,4-Dichlorobenzyl)-3-morpholinoindole-2-carboxylic acid (Compound 72)**

Trifluoroacetic acid (5 ml) was added to a solution of *t*-butyl *N*-(3,4-dichlorobenzyl)-3-morpholinoindole-2-carboxylate (293 mg) in dichloromethane (10 ml) and the reaction stirred at ambient temperature overnight. The reaction was concentrated *in vacuo* and the residue purified by column chromatography using 20% ethyl acetate : *iso*-hexane as eluent to afford the product as a brown solid (125 mg, 30%); NMR d (CD_3SOCD_3) 3.10 (t, 4H), 3.83 (t, 4H), 5.36 (s, 2H), 7.01 (t, 1H), 7.12 (m, 2H), 7.46 (m, 2H), 7.58 (m, 2H), *M*/z(-) 404.2 ($M-H^+$).

Example 22

Compound 48

Acetic anhydride (0.4 g) was added to a stirred solution of *N*-(3,4-dichlorobenzyl)-2-carboxy-3-indoleacetic acid (0.1 g) in dry DCM (5 mls) under an inert atmosphere and heated to 50°C for 4 hours. The reaction was cooled, concentrated *in vacuo* and toluene added before reducing *in vacuo* again. The resultant yellow solid was dissolved in DCM under an inert atmosphere before morpholine (0.6 mls) was added and the reaction was stirred for 48 hours at ambient temperature. Combined organic extracts were washed with aqueous hydrochloric acid (2.0 M, 5 ml), water and saturated aqueous sodium chloride solution before concentration

in vacuo. The residue was dissolved in saturated aqueous sodium hydrogen orthophosphate and acidified by the addition of aqueous hydrochloric acid (2.0 M, 5 ml) causing the precipitation of the product as a light brown solid. (0.098 g, 83%); NMR d (CD_3SOCD_3) 3.51 (brs, 2H), 3.60 (M, 4H), 3.71 (brs, 2H), 4.23 (s, 2H), 5.88 (s, 2H), 6.99 (d, 1H), 7.19 (t, 1H), 7.32 - 7.40 (m, 2H), 7.56 - 7.63 (m, 2H), 7.78 (d, 1H); *M*/z (-) 445 (*M*-H^+).

Example 23

The procedure described in Example 22 above was repeated using the appropriate amines. Thus were obtained the compounds described below.

Compound 49

69% yield; NMR d (CD_3SOCD_3) 3.11 (dd, 2H), 3.38 (t, 2H), 3.96 (s, 2H), 5.78 (s, 2H), 6.91 (dd, 1H), 7.12 (t, 1H), 7.24 - 7.35 (m, 2H), 7.44 - 7.53 (m, 2H), 7.72 (d, 1H), 8.02 (M, 1H); *M*/z (-) 419 (*M*-H^+).

Compound 52

44% yield; *M*/z (-) 433 (*M*-H^+).

Compound 53

32% yield; *M*/z (-) 469 (*M*-H^+).

Compound 54

69% yield; *M*/z (-) 486 (*M*-H^+).

Compound 55

42% yield; *M*/z (-) 491 (*M*-H^+).

Compound 56

38% yield; *M*/z (-) 433 (*M*-H^+).

Comp und 57

58% yield; *M*/z (-) 459 (*M*-H^+).

Compound 58

12% yield; *M*/z (-) 544 (*M*-H$^+$).

Compound 59

52% yield; *M*/z (-) 459 (*M*-H$^+$).

Compound 60

21% yield; *M*/z (-) 515 (*M*-H$^+$).

Compound 61

25% yield; *M*/z (-) 558 (*M*-H$^+$).

Compound 62

18% yield; *M*/z (-) 489 (*M*-H$^+$).

Compound 63

19% yield; *M*/z (-) 509 (*M*-H$^+$).

Compound 64

10% yield; *M*/z (-) 495 (*M*-H$^+$).

Compound 65

18% yield; *M*/z (-) 469 (*M*-H$^+$).

Example 24

Compound 8

3,5-Dimethylisoxazole-4-sulphonyl chloride (0.097g) in dichloromethane (2 ml) was added to a stirred solution of ethyl 3-amino-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (0.15 g) in dichloromethane (3 ml). Pyridine (0.036 g) was added and the reaction was stirred for 16 hours at ambient temperature. The reaction mixture was washed with aqueous citric acid (1.0M, 4 ml), saturated aqueous sodium hydrogencarbonate solution and water and

concentrated *in vacuo*. The residue was dissolved in THF (5 ml) and LiOH (2M, 3 ml) added and the reaction stirred for 16 hours. The reaction was then concentrated *in vacuo* and the residue dissolved in water. The solution was acidified by dropwise addition of acetic acid, resulting in the precipitation of a white solid which was filtered, washed with water and dried *in vacuo* to give the desired end product as a white solid. (75 mg, 37%, 2 steps); NMR d (CD_3SOCD_3) 2.00 (s, 3H), 2.07 (s, 3H), 5.74 (s, 2H), 6.93 (dd, 1H), 7.17 (t, 1H), 7.24 (d, 1H), 7.34 (t, 1H), 7.55 (dd, 2H), 7.66 (d, 1H), 9.72 (brs, 1H); *M*/z (-) 492 (*M*-H^+).

Example 25

The procedure described in Example 24 above was repeated using the appropriate acid chloride. Thus were obtained the compounds described below.

Compound 9

48% yield (2 steps); NMR d (CD_3SOCD_3) 2.00 (s, 3H), 2.14 (s, 3H), 5.71 (s, 2H), 6.77 (d, 1H), 7.12 (t, 1H), 7.26 - 7.37 (m, 2H), 7.45 (d, 1H), 7.52 (d, 1H), 7.63 (d, 1H), 9.58 (brs, 1H), 12.39 (s, 1H); *M*/z (-) 551 (*M*-H^+).

Compound 10

66% yield (2 steps); NMR d (CD_3SOCD_3) 3.56 (s, 3H), 5.71 (s, 2H), 6.82 (dd, 1H), 7.07 (t, 1H), 7.21 - 7.30 (m, 2H), 7.45 - 7.55 (m, 3H), 7.66 - 7.73 (m, 2H), 9.10 (s, 1H); *M*/z (-) 477 (*M*-H^+).

Compound 11

69% yield (2 steps); NMR d (CD_3SOCD_3) 4.10 (s, 2H), 5.79 (s, 2H), 6.93 (dd, 1H), 7.18 (t, 1H), 7.29 - 7.36 (m, 2H), 7.50 - 7.59 (m, 2H), 7.81 (d, 1H); *M*/z (-) 455 (*M*-H^+).

Compound 12

14% yield (2 steps); NMR d (CD_3SOCD_3) 1.94 (s, 3H), 3.61 (s, 3H), 5.70 (s, 2H), 6.84 (dd, 1H), 7.12 (t, 1H), 7.27 - 7.34 (m, 2H), 7.52 (t, 2H), 7.61 (d, 1H), 9.28 (brs, 1H); *M*/z (-) 525, 527, 529 (*M*-H^+).

Compound 13

79% yield (2 steps); NMR d (CD_3SOCD_3) 3.49 (s, 3H), 5.68 (s, 2H), 6.79 (dd, 1H), 7.13 (t, 1H), 7.19 (d, 1H), 7.30 (t, 1H), 7.50 - 7.56 (m, 2H), 7.59 - 7.77 (m, 3H), 7.91 (t, 1H), 8.23 (d, 1H), 8.87 (brs, 1H); *M*/z (-) 551 (*M*-H^+).

Compound 14

36% yield (2 steps); NMR d (CD_3SOCD_3) 3.46 (s, 2H), 5.79 (s, 2H), 6.91 (dd, 1H), 7.09 (t, 1H), 7.25 - 7.35 (m, 2H), 7.50 - 7.58 (m, 2H), 7.62 (d, 1H), 9.89 (brs, 1H).

Compound 15

90% yield (2 steps); NMR d (CD_3SOCD_3) 2.10 (s, 3H), 2.67 (m, 2H), 2.76 (m, 2H), 5.79 (s, 2H), 6.92 (dd, 1H), 7.10 (t, 1H), 7.28 - 7.33 (m, 2H), 7.50 - 7.56 (m, 2H), 7.61 (d, 1H), 9.67 (s, 1H); *M*/z (-) 435 (*M*-H^+).

Compound 16

73% yield (2 steps); NMR d (CD_3SOCD_3) 3.96 (s, 2H), 5.79 (s, 2H), 6.90 (s, 1H), 6.94 - 7.13 (m, 3H), 7.26 - 7.34 (m, 3H), 7.38 (d, 1H), 7.48 - 7.59 (m, 3H), 9.86 (s, 1H), 13.36 (brs, 1H); *M*/z (-) 457 (*M*-H^+).

Compound 17

53% yield (2 steps); NMR d (CD_3SOCD_3) 1.36 (d, 3H), 4.20 (m, 1H), 5.79 (s, 2H), 6.00 (d, 1H), 6.88 (dd, 1H), 7.07 (t, 1H), 7.28 - 7.35 (m, 2H), 7.50 - 7.56 (m, 2H), 7.99 (d, 1H), 10.21 (brs, 1H); *M*/z (-) 405 (*M*-H^+).

Compound 18

73% yield (2 steps); NMR d (CD_3SOCD_3) 3.83 (s, 6H), 5.81 (s, 2H), 6.95 (dd, 1H), 7.06 - 7.17 (m, 2H), 7.30 - 7.37 (m, 2H), 7.51 - 7.61 (m, 3H), 7.66 (dd, 1H), 7.75 (d, 1H), 10.08 (brs, 1H); *M*/z (-) 497 (*M*-H^+).

Compound 19

66% yield (2 steps); NMR d (CD_3SOCD_3) 2.04 (s, 3H), 5.68 (s, 2H), 6.60 (dd, 1H), 7.12 (d, 1H), 7.20 (d, 1H), 7.28 (t, 1H), 7.40 (d, 2H), 7.47 (d, 2H), 7.62 (d, 2H), 7.72 (d, 1H), 9.13 (s, 1H), 10.27 (s, 1H); *M*/z (-) 530 (*M*-H^+).

Compound 20

47% yield (2 steps); NMR d (CD_3SOCD_3) 5.78 (s, 2H), 6.86 (dd, 1H), 7.10 - 7.18 (m, 3H), 7.21 (d, 1H), 7.31 (t, 1H), 7.54 (dd, 1H), 7.63 (d, 1H), 9.80 (brs, 1H); *M*/z (-) 517 (*M*-H^-), 515, 513.

Compound 22

40% yield (2 steps); NMR d (CD_3SOCD_3) 4.69 (s, 2H), 5.76 (s, 2H), 6.84 (dd, 1H), 7.14 (t, 1H), 7.23 - 7.40 (m, 3H), 7.46 - 7.67 (m, 3H), 7.85 (d, 1H), 10.13 (brs, 1H); *M*/z (-) 546 (*M*-H^+).

Example 26

Methyl ester of Compound 1

To a solution of methyl 3-amino-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (253 mg) in tetrahydrofuran (8 ml) was added triethylamine (0.15 ml) followed by a solution of 3-chlorobenzoyl chloride (153 mg) in tetrahydrofuran (2 ml). The resulting mixture was stirred at room temperature for 4 hours. The mixture was partitioned between water (10 ml) and ethyl acetate (20 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography using *iso*-hexane : 20% ethyl acetate as eluent to give the product (259 mg, 74%); NMR d ($CDCl_3$) 3.9 (s, 3H), 5.7 (s, 2H), 6.8 (d, 1H), 7.2 - 7.6 (m, 7H), 7.9 (d, 1H), 8.05 (s, 1H), 8.3 (d, 1H), 10.1 (brs, 1H); *M/z* (-) 487.1 (M^-), 485.0.

Example 27

The procedure described in Example 26 above was repeated using the appropriate acid chloride. Thus was obtained the compound described below.

Methyl ester of Compound 2

37% yield; NMR d ($CDCl_3$) 2.95 (s, 3H), 3.95 (s, 3H), 5.7 (s, 2H), 6.8 (dd, 1H), 7.1 - 7.5 (m, 4H), 7.7 (s, 1H), 8.15 (d, 1H); *M/z* (-) 427.3 (M^-), 425.3.

Example 28

Ethyl *N*-(3,4-dichlorobenzyl)-3-(tetrahydrofurfurylcarbamoyl)indole-2-carboxylate (Ethyl ester of Compound 68)

To a stirred solution of ethyl *N*-(3,4-dichlorobenzyl)-2-ethoxycarbonylindole-3-carboxylic acid (100 mg) in dichloromethane (4 ml) at ambient temperature, under argon, was added DMF (1 drop) and oxalyl chloride in dichloromethane (2M, 153µl). The reaction was stirred at ambient temperature for 7 hours, then concentrated *in vacuo* and dissolved in dichloromethane (4 ml). Tetrahydrofurfurylamine (53 µl) was added, followed by triethylamine (71 µl) and the reaction stirred under argon for 16 hours. The reaction was diluted with dichloromethane (30 ml), washed with HCl (2M, 30 ml) and water (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude residue which was purified by column chromatography, using ethyl acetate : *iso*-hexane as eluent (gradient 10/90 - 50/50), to give the product as an off-white solid (57 mg, 47%); *M*/z (+) 475.3 (MH^+).

Example 29

Ethyl *N*-(3,4-dichlorobenzyl)-3-(1,1-dioxidotetrahydrothiophene-3-carbamoyl)indole-2-carboxylate (Ethyl ester of Compound 81)

Ethyl *N*-(3,4-dichlorobenzyl)-2-ethoxycarbonylindole-3-carboxylic acid (104 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (76 mg), 3-aminotetrahydrothiophene 1,1-dioxide (36 mg) and 4-dimethylaminopyridine (5 mg) in dichloromethane (10 ml) were stirred at ambient temperature under argon for 16 hours. The crude reaction mixture was purified by column chromatography using ethyl acetate : *iso*-hexane as eluent (gradient 0/100 - 75/25), to give the product as a white solid (32 mg, 24%); *M*/z (+) 509.4 (MH^+).

Example 30

The procedure described in Example 29 above was repeated using the appropriate amines. Thus were obtained the compounds described below.

Ethyl *N*-(3,4-dichlorobenzyl)-3-(1,1-dioxidothiomorpholinocarbonyl)indole-2-carboxylate (Ethyl ester of Compound 84)

48% yield; *M*/z (+) 509.1 (MH^+).

Ethyl *N*-(3,4-dichlorobenzyl)-3-(3,5-dimethylisoxazol-4-ylmethylcarbamoyl)indole-2-carboxylate (Ethyl ester of Compound 85)

40% yield; *M*/z(+) 500.1 (MH^+).

Example 31

Ethyl (Z)-*N*-(3,4-dichlorobenzyl)-2-ethoxycarbonylindole-3-acrylic acid (Ethyl ester of Compound 50)

Malonic acid (106 mg) and piperidine (1 drop) were added to a solution of ethyl 3-formyl-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (315 mg) in pyridine (5 ml) and the reaction stirred at 100°C overnight. The reaction was concentrated *in vacuo* and the residue dissolved in ethyl acetate (30 ml), washed with HCl (2M, 30 ml) and water (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was triturated with a mixture of dichloromethane, ethyl acetate and hexane to give the product as a tan coloured solid (68 mg, 19%); NMR d (CD_3SOCD_3) 1.25 (t, 3H), 4.35 (q, 2H), 5.80 (s, 2H), 6.55 (d, 1H), 6.90 (m, 1H), 7.25 - 7.45 (m, 3H), 7.50 (m, 1H), 7.60 (m, 1H), 8.05 (m, 1H), 8.35 (d, 1H) 12.24 (s, 1H); *M*/(-) 416.4 (M-H^+).

Example 32

Biological Assays for hMCP-1 Antagonists

The following biological test methods, data and Examples serve to illustrate the present invention.

Abbreviations:

ATCC	American Type Culture Collection, Rockville, USA.
BCA	Bicinchroninic acid, (used, with copper sulphate, to assay protein)
BSA	Bovine Serum Albumin
DMEM	Dulbecco's modified Eagle's medium

EGTA	Ethylenebis(oxyethylenenitrilo)tetraacetic acid
FCS	Foetal calf serum
HEPES	(N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid])
HBSS	Hank's Balanced Salt Solution
hMCP-1	Human Monocyte Chemoattractant Protein-1
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction

AMPLITAQ™, available from Perkin-Elmer Cetus, is used as the source of thermostable DNA polymerase.

Binding Buffer is 50 mM HEPES, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.5% foetal calf serum, adjusted to pH 7.2 with 1 M NaOH.

Non-Essential Amino Acids (100X concentrate) is: L-Alanine, 890 mg/l; L-Asparagine, 1320 mg/l; L-Aspartic acid, 1330 mg/l; L-Glutamic acid, 1470 mg/l; Glycine, 750 mg/l; L-Proline, 1150 mg/l and; L-Serine, 1050 mg/l.

Hypoxanthine and Thymidine Supplement (50x concentrate) is: hypoxanthine, 680 mg/l and; thymidine, 194 mg/l.

Penicillin-Streptomycin is: Penicillin G (sodium salt); 5000 units/ml; Streptomycin sulphate, 5000 µg/ml.

Human monocytic cell line THP-1 cells are available from ATCC, accession number ATCC TIB-202.

Hank's Balanced Salt Solution (HBSS) was obtained from Gibco; see *Proc. Soc. Exp. Biol. Med.*, 1949, **71**, 196.

Synthetic cell culture medium, RPMI 1640 was obtained from Gibco; it contains inorganic salts [$Ca(NO_3)_2.4H_2O$ 100 mg/l; KCl 400 mg/l; $MgSO_4.7H_2O$ 100 mg/l; NaCl 6000 mg/l; $NaHCO_3$ 2000 mg/l & Na_2HPO_4 (anhyd) 800 mg/l], D-Glucose 2000 mg/l, reduced glutathione 1 mg/l, amino acids and vitamins.

FURA-2/AM is 1-[2-(5-carboxyoxazol-2-yl)-6-aminobenzofuran-5-oxy]-2-(2'-amino-5'-methylphenoxy)-ethane-*N*,*N*,*N'*,*N'*-tetraacetic acid pentaacetoxymethyl ester and was obtained from Molecular Probes, Eugene, Oregon, USA.

Blood Sedimentation Buffer contains 8.5g/l NaCl and 10g/l hydroxyethyl cellulose.

Lysis Buffer is 0.15M NH_4Cl^-, 10mM $KHCO_3$, 1mM EDTA

Whole Cell Binding Buffer is 50 mM HEPES, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.5% BSA, 0.01% NaN_3, adjusted to pH 7.2 with 1M NaOH.

Wash buffer is 50mM HEPES. 1mM $CaCl_2$, 5mM $MgCl_2$, 0.5% heat inactivated FCS, 0.5MNaCl adjusted to pH7.2 with 1M NaOH.

General molecular biology procedures can be followed from any of the methods described in "Molecular Cloning - A Laboratory Manual" Second Edition, Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory, 1989).

i) Cloning and expression of hMCP-1 receptor

The MCP-1 receptor B (CCR2B) cDNA was cloned by PCR from THP-1 cell RNA using suitable oligonucleotide primers based on the published MCP-1 receptor sequences (Charo *et al.*, 1994, *Proc. Natl. Acad. Sci. USA*, **91**, 2752). The resulting PCR products were cloned into vector PCR-II™ (InVitrogen, San Diego, CA.). Error free CCR2B cDNA was subcloned as a Hind III-Not I fragment into the eukaryotic expression vector pCDNA3 (InVitrogen) to generate pCDNA3/CC-CKR2A and pCDNA3/CCR2B respectively.

Linearised pCDNA3/CCR2B DNA was transfected into CHO-K1 cells by calcium phosphate precipitation (Wigler *et al.*, 1979, *Cell*, **16**, 777). Transfected cells were selected by the addition of Geneticin Sulphate (G418, Gibco BRL) at 1mg/ml, 24 hours after the cells had been transfected. Preparation of RNA and Northern blotting were carried out as described previously (Needham *et al.*, 1995, *Prot. Express. Purific.*, **6**, 134). CHO-K1 clone 7 (CHO-CCR2B) was identified as the highest MCP-1 receptor B expressor.

ii) Preparation of membrane fragments

CHO-CCR2B cells were grown in DMEM supplemented with 10% foetal calf serum, 2 mM glutamine, 1x Non-Essential Amino Acids, 1x Hypoxanthine and Thymidine Supplement and Penicillin-Streptomycin (at 50 µg streptomycin/ml, Gibco BRL). Membrane fragments were prepared using cell lysis/differential centrifugation methods as described previously (Siciliano *et al.*, 1990, *J. Biol. Chem.*, **265**, 19658). Protein concentration was estimated by BCA protein assay (Pierce, Rockford, Illinois) according to the manufacturer's instructions.

iii) Assay

^{125}I MCP-1 was prepared using Bolton and Hunter conjugation (Bolton *et al.*, 1973, *Biochem. J.*, **133**, 529; Amersham International plc]. Equilibrium binding assays were carried out using the method of Ernst *et al.*, 1994, *J. Immunol.*, **152**, 3541. Briefly, varying amounts

of ^{125}I-labeled MCP-1 were added to 7μg of purified CHO-CCR2B cell membranes in 100 μl of Binding Buffer. After 1 hour incubation at room temperature the binding reaction mixtures were filtered and washed 5 times through a plate washer (Brandel MLR-96T Cell Harvester) using ice cold Binding Buffer. Filter mats (Brandel GF/B) were pre-soaked for 60 minutes in 0.3% polyethylenimine prior to use. Following filtration individual filters were separated into 3.5ml tubes (Sarstedt No. 55.484) and bound ^{125}I-labeled MCP-1 was determined (LKB 1277 Gammamaster). Cold competition studies were performed as above using 100 pM ^{125}I-labeled MCP-1 in the presence of varying concentrations of unlabelled MCP-1. Non-specific binding was determined by the inclusion of a 200-fold molar excess of unlabelled MCP-1 in the reaction.

Ligand binding studies with membrane fragments prepared from CHO-CCR2B cells showed that the CCR2B receptor was present at a concentration of 0.2 pmoles/mg of membrane protein and bound MCP-1 selectively and with high affinity (IC_{50} = 110 pM, K_d =120 pM). Binding to these membranes was completely reversible and reached equilibrium after 45 minutes at room temperature, and there was a linear relationship between MCP-1 binding and CHO-CCR2B cell membrane concentration when using MCP-1 at concentrations between 100 pM and 500 pM.

Test compounds dissolved in DMSO (5μl) were tested in competition with 100 pM labelled MCP-1 over a concentration range (0.01-50μM) in duplicate using eight point dose-response curves and IC_{50} concentrations were calculated.

Compounds tested of the present invention had IC_{50} values of 50μM or less in the hMCP-1 receptor binding assay described herein. For example Compound 81 had an IC_{50} of 6.86μM.

b) MCP-1 mediated calcium flux in THP-1 cells

The human monocytic cell line THP-1 was grown in a synthetic cell culture medium RPMI 1640 supplemented with 10 % foetal calf serum, 6mM glutamine and Penicillin-Streptomycin (at 50 μg streptomycin/ml, Gibco BRL). THP-1 cells were washed in HBSS (lacking Ca^{2+} and Mg^{2+}) + 1 mg/ml BSA and resuspended in the same buffer at a density of 3 x 10^6 cells/ml. The cells were then loaded with 1mM FURA-2/AM for 30 min at 37°C, washed twice in HBSS, and resuspended at 1x10^6 cells/ml. THP-1 cell suspension (0.9 ml) was added to a 5 ml disposable cuvette containing a magnetic stirrer bar and 2.1 ml of prewarmed (37°C) HBSS containing 1 mg/ml BSA, 1 mM $MgCl_2$ and 2 mM $CaCl_2$. The

cuvette was placed in a fluorescence spectrophotometer (Perkin Elmer, Norwalk, CT) and preincubated for 4 min at 37°C with stirring. Fluorescence was recorded over 70 sec and cells were stimulated by addition of hMCP-1 to the cuvette after 10 sec. $[Ca^{2+}]i$ was measured by excitation at 340 nm and 380 nm alternately and subsequent measurement of the intensity of the fluorescence emission at 510 nm. The ratio of the intensities of the emitted fluorescent light following excitation at 340 nm and 380 nm, (R), was calculated and displayed to give and estimate of cytoplasmic $[Ca^{2+}]$ according to the equation:-

$$[Ca^{2+}]i = K_d \frac{(R-Rmin)}{(Rmax-R)} (Sf2/Sb2)$$

where the K_d for FURA-2 Ca^{2+} complex at 37°C was taken to be 224nm. R_{max} is the maximal fluorescence ratio determined after addition of 10 mM Ionomycin, R_{min} is the minimal ratio determined by the subsequent addition of a Ca^{2+} free solution containing 5 mM EGTA, and Sf2/Sb2 is the ratio of fluorescence values at 380 nm excitation determined at R_{min} and R_{max}, respectively.

Stimulation of THP-1 cells with hMCP-1 induced a rapid, transient rise in $[Ca^{2+}]i$ in a specific and dose dependent manner. Dose response curves indicated an approximate EC_{50} of 2 nm. Test compounds dissolved in DMSO (10µl) were assayed for inhibition of calcium release by adding them to the cell suspension 10 sec prior to ligand addition and measuring the reduction in the transient rise in $[Ca^{2+}]i$. Test compounds were also checked for lack of agonist activity by addition in place of hMCP-1.

c) hMCP-1 and RANTES mediated chemotaxis.

In vitro chemotaxis assays were performed using the human monocytic cell line THP-1. Cell migration through polycarbonate membranes was measured by enumerating those passing through either directly by Coulter counting or indirectly by use of a colourimetric viability assay measuring the cleavage of a tetrazolium salt by the mitochondrial respiratory chain (Scudiero D.A. *et al.* 1988, *Cancer Res.*, **48**, 4827-4833).

Chemoattractants were introduced into a 96-well microtitre plate which forms the lower well of a chemotaxis chamber fitted with a PVP-free 5 µm poresize polycarbonate adhesive framed filter membrane (NeuroProbe MB series, Cabin John, MD 20818, USA) according to the manufacturer's instructions. The chemoattractant was diluted as appropriate in synthetic cell culture medium, RPMI 1640 (Gibco) or supplemented with 2 mM glutamine and 0.5% BSA, or alternatively with HBSS with Ca^{2+} and Mg^{2+} without Phenol Red (Gibco)

plus 0.1% BSA. Each dilution was degassed under vacuum for 30 min and was placed (400 µl) in the lower wells of the chamber and THP-1 cells ($5x10^5$ in 100 µl RPMI 1640 + 0.5%BSA) were incubated in each well of the upper chamber. For the inhibition of chemotaxis the chemoattractant was kept at a constant submaximal concentration determined previously (1nM MCP-1) and added to the lower well together with the test compounds dissolved in DMSO (final DMSO concentration < 0.05% v/v) at varying concentrations. The chamber was incubated for 2 h at 37°C under 5 % CO_2. The medium was removed from the upper wells which were then washed out with 200 µl physiological saline before opening the chamber, wiping dry the membrane surface and centrifuging the 96-well plate at 600 g for 5 min to harvest the cells. Supernatant (150 µl) was aspirated and 10 µl of cell proliferation reagent, WST-1, {4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-phenyl disulfonate} plus an electron coupling reagent (Boehringer Mannheim, Cat.no. 1644 807) was added back to the wells. The plate was incubated at 37°C for 3 h and the absorbance of the soluble formazan product was read on a microtitre plate reader at 450 nm. The data was input into a spreadsheet, corrected for any random migration in the absence of chemoattractant and the average absorbance values, standard error of the mean, and significance tests were calculated. hMCP-1 induced concentration dependent cell migration with a characteristic biphasic response, maximal 0.5-1.0 nm.

In an alternative form of the above assay, fluorescently tagged cells can be used in order to assist in end point detection. In this case, the THP-1 cells used are fluorescently tagged by incubation in the presence of 5mM Calcein AM (Glycine, N,N'-[[3',6'-bis(acetyloxy)-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthene]-2',7'-diyl]bis(methylene)] bis[N-[2-[(acetyloxy)methoxy]-2-oxoethyl]]-bis[(acetyloxy)methyl] ester; Molecular Probes) for 45 minutes in the dark. Cells are harvested by centrifugation and resuspended in HBSS (without Phenol Red) with Ca^{2+}, Mg^{2+} and 0.1% BSA. 50µl (2x105 cells) of the cell suspension are placed on the filter above each well and, as above, the unit is incubated at 37°C for 2 hours under 5% CO_2. At the end of the incubation, cells are washed off the upper face of the filter with phosphate buffered saline, the filter removed from the plate and the number of cells attracted to either the underside of the filter or the lower well estimated by reading fluorescence at 485nm excitation, 538nm emission wavelengths (fmax, Molecular Devices). The data was input into a spreadsheet, corrected for any random migration in the absence of chemoattractant and the average fluorescence values, standard error of the mean, percentage

inhibition and IC_{50} of compounds under test and significance tests can be calculated. In addition to MCP-1 induced chemotaxis, this alternative form of the assay was also used to measure inhibition of RANTES (2nM) induced chemotaxis.

d) Binding to human peripheral blood mononuclear cells(PBMCs)

i) Preparation of human PBMCs

Fresh human blood (200ml) was obtained from volunteer donors, collected into sodium citrate anticoagulant to give a final concentration of 0.38%. The blood was mixed with Sedimentation Buffer and incubated at 37°C for 20 minutes. The supernatant was collected and centrifuged at 1700rpm for 5 minutes (Sorvall RT6000D). The pellet obtained was resuspended in 20 ml RPMI/BSA (1mg/ml) and 4 x 5mls of cells were carefully layered over 4 x 5mls of Lymphoprepä (Nycomed) in 15ml centrifuge tubes. Tubes were spun at 1700rpm for 30 minutes (Sorvall RT6000D) and the resultant layer of cells was removed and transferred to 50ml Falcon tubes. The cells were washed twice in Lysis Buffer to remove any remaining red blood cells followed by 2 washes in RPMI/BSA. Cells were resuspended in 5mls of Binding Buffer. Cell number was measured on a Coulter counter and additional binding buffer was added to give a final concentration of $1.25x10^7$ PBMCs /ml.

ii) Assay

[^{125}I]MCP-1 was prepared using Bolton and Hunter conjugation (Bolton *et al.*, 1973, *Biochem. J.*, **133**, 529; Amersham International plc]. Equilibrium binding assays were carried out using the method of Ernst *et al.*, 1994, *J. Immunol.*, **152**, 3541. Briefly, 50µl of ^{125}I-labeled MCP-1 (final concentration 100pM) was added to 40µl ($5x10^5$ cells) of cell suspension in a 96 well plate. Compounds, diluted in Whole Cell Binding Buffer from a stock solution of 10mM in DMSO were added in a final volume of 5µl to maintain a constant DMSO concentration in the assay of 5%. Total binding was determined in the absence of compound. Non-specific binding was defined by the addition of 5µl cold MCP-1 to give a final assay concentration of 100nM. Assay wells were made up to a final volume of 100µl with Whole Cell Binding Buffer and the plates sealed. Following incubation at 37°C for 60 minutes the binding reaction mixtures were filtered and washed for 10 seconds using ice cold Wash Buffer using a plate washer (Brandel MLR-96T Cell Harvester). Filter mats (Brandel GF/B) were pre-soaked for 60 minutes in 0.3% polyethylenimine plus 0.2% BSA prior to use. Following filtration individual filters were separated into 3.5ml tubes (Sarstedt No. 55.484) and bound ^{125}I-labeled MCP-1 was determined (LKB 1277 Gammamaster).

Test compound potency was determined by assay in duplicate using six point dose-response curves and IC_{50} concentrations were determined.

For example, using this method, compound No. 14 in Table I showed an IC_{50} of 11.4μM in the hMCP-1 chemotaxis assay and compound No.23 in Table 1 showed an IC_{50} of 2.95μM in the RANTES chemotaxis assay.

No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention.

Example 33

Pharmaceutical Compositions

The following Example illustrates, but is not intended to limit, pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X.	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium	1.5

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	to adjust pH to 7.6
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f)

Injection II	(10 mg/ml)
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

(g)

Injection III	(1mg/ml, buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

(h)

Aerosol I	mg/ml
Compound X	10.0
Sorbitan trioleate	13.5
Trichlorofluoromethane	910.0
Dichlorodifluoromethane	490.0

(i)

Aerosol II	mg/ml
Compound X	0.2
Sorbitan trioleate	0.27
Trichlorofluoromethane	70.0
Dichlorodifluoromethane	280.0
Dichlorotetrafluoroethane	1094.0

(j)

Aerosol III	mg/ml
Compound X	2.5
Sorbitan trioleate	3.38
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(k)

Aerosol IV	mg/ml
Compound X	2.5
Soya lecithin	2.7
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(l)

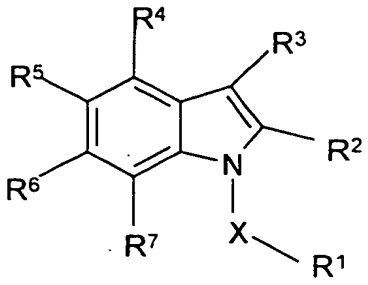
Ointment	ml
Compound X	40 mg
Ethanol	300 µl
Water	300 µl
1-Dodecylazacycloheptan-2-one	50 µl
Propylene glycol	to 1 ml

Note:

Compound X in the above formulation may comprise a compound illustrated in Examples herein. The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

Claims

1. The use of a compound of formula (I)



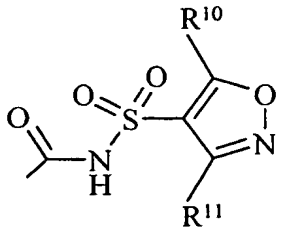
(I)

or a pharmaceutically acceptable salt, amide or ester thereof;

X is CH_2 or SO_2

R^1 is an optionally substituted aryl or heteroaryl ring;

R^2 is carboxy, cyano, $-C(O)CH_2OH$, $-CONHR^8$, $-SO_2NHR^9$, tetrazol-5-yl, SO_3H, or a group of formula (VI)



(VI)

where R^8 is selected from hydrogen, alkyl, aryl, cyano, hydroxy, $-SO_2R^{12}$ where R^{12} is alkyl, aryl, heteroaryl, or haloalkyl, or R^8 is a group $-(CHR^{13})_r-COOH$ where r is an integer of 1-3 and each R^{13} group is independently selected from hydrogen or alkyl; R^9 is hydrogen, alkyl, optionally substituted aryl such as optionally substituted phenyl or optionally subtituted heteroaryl such as 5 or 6 membered heteroaryl groups, or a group COR^{14} where R^{14} is alkyl, aryl, heteroaryl or haloalkyl; R^{10} and R^{11} are independently selected from hydrogen or alkyl, particularly C_{1-4} alkyl;

R^3 is a group OR^{15}, $S(O)_qR^{15}$, $NHCOR^{16}$, $NHSO_2R^{16}$, $(CH_2)_sCOOH$, $(CH_2)_tCONR^{17}R^{18}$, $NR^{17}R^{18}$, $SO_2NR^{17}R^{18}$ or optionally substituted alkenyl, where q is 0, 1 or 2, s is 0 or an integer of from 1 to 4, t is 0 or an integer of from 1 to 4, R^{15} is a substituted alkyl or cycloalkyl group or an optionally substituted heteroaryl group , R^{16} is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl and R^{17} and R^{18} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl and optionally substituted heteroaryl, with the proviso that at least one of R^{17} or R^{18} is other than hydrogen, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms; and

R^4, R^5, R^6 and R^7 are independently selected from hydrogen, a functional group or an optionally substituted hydrocarbyl groups or optionally substituted heterocyclic groups, provided that R^4 is other than a group , $OR^{18'}$, $S(O)_mR^{18'}$, $NR^{19}R^{20}$, $C(O)NR^{19}R^{20}$, $NHCOR^{18}$, $NHSO_2R^{18}$or $OCONR^{19}R^{20}$ or an alkyl group subsituted by OR^{18}, $S(O)_mR^{18}$, $NR^{19}R^{20}$ where R^{18} , R^{19} and R^{20} are independently selected from hydrogen or optionally substituted hydrocarbyl, or R^{19} and R^{20} together with the atom to which they are attached, form an optionally substituted heterocyclyl ring as defined above which optionally contains further heteroatoms such as $S(O)_n$, oxygen and nitrogen, m is 0 or an integer of 1-3 and $R^{18'}$ is a substituted hydrogen-containing alkyl group,

for use in the preparation of a medicament for the inhibition of monocyte chemoattractant protein-1 and/or RANTES induced chemotaxis.

2. The use according to claim 1 wherein in the compound of formula (I), R^4 is hydrogen, hydroxy, halo, alkoxy, aryloxy or an optionally substituted hydrocarbyl group or optionally substituted heterocyclic group.

3. The use according to any one of the preceding claims Particular groups R^3 include OR^{15}, $S(O)_qR^{15}$, $NHCOR^{16}$, $NHSO_2R^{16}$, $SO_2NR^{17}R^{18}$ where q, R^{15}, R^{16}, R^{17} and R^{18} are as defined in claim 1.

4. The use according to any one of the preceding claims wherein R^3 is a group of formula $-O(CH_2)_a[(CHOH)(CH_2)_b]_d CH_2OH$ where a is 0 or an integer of from 1 to 4, b is 0 or an integer of from 1 to 3, and d is 0, or 1.

5. The use according to any one of the preceding claims wherein R^1 is 3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 3-chloro-4-fluorophenyl or 2,3-dichloropyrid-5-yl.

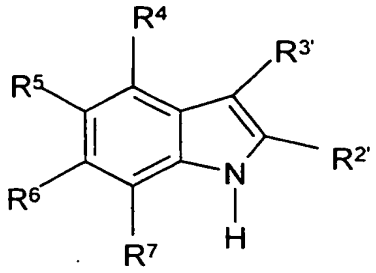
6. The use according to any one of the preceding claims where X is CH_2.

7. A compound for use in therapy, said compound comprising a compound of formula (1A) which is a compound of formula (I) as defined in claim 1 subject to the following provisos:
(i) when R^2 is carboxy or a salt or amide thereof, at least three of R^4, R^5, R^6 and R^7 are hydrogen, and R^3 is $S(O)qR^{15}$, R^{15} is other than C_{1-4} alkyl substituted by carboxy or an ester or amide derivative thereof;
(ii) when R^3 is a group $NHCOR^{16}$ or $NHSO_2R^{16}$, R^{16} is optionally substituted alkyl; and
(iii) where R^3 is a group SR^{14} where R^{14} is 2-quinolylmethyl, R^2 is COOH or an ethyl ester thereof, each of R^4, R^5, and R^7 are hydrogen, R^1 is 4-chlorophenyl, R^6 is other than 2-quinolylmethyl.

8. A pharmaceutical compositions comprising a compound of formula (IA) as defined in claim 7 in combination with a pharmaceutically acceptable carrier.

9. A compound of formula (IB) which is a compound of formula (IA) as defined in claim 7, subject to the following further provisos:
(iv) where R^3 is a group COOH or CH_2COOH, R^2 is COOH and each of R^4, R^5, R^6 and R^7 are hydrogen, R^1 is other than unsubsituted phenyl; and
(v) where R^3 is a group CH_2COOH, R^2 is COOH and each of R^4, R^5, and R^7 are hydrogen, R^1 is 4-chlorophenyl, R^6 is other than methoxy; and
(vi) when R^3 is OR^{15} or $S(O)_qR^{15}$, R^{15} is other than C_{1-6} haloalkyl: and
(vii) when R^2 is $COOCH_2CH_3$, each of R^4, R^5, R^6 and R^7 are hydrogen, and R^1 is 4-chlorophenyl, then R^3 is other than a group $CH=CH(CN)_2$.

10. A method of preparing a compound of formula (I) as defined in claim 1, which method comprises reacting a compound of formula (VII)



(VII)

where R^4, R^5, R^6 and R^7 are as defined in relation to formula (I), $R^{2'}$ is a group R^2 as defined in relation to formula (I) or a protected form thereof, and $R^{3'}$ is a group R^3 as defined in relation to formula (I) or a precursor thereof ; with compound of formula (VIII)

$$R^1\text{-}X\text{-}Z^1$$

(VIII)

where R^1 and X are as defined in relation to formula (I) and Z^1 is a leaving group; and thereafter if desired or necessary carrying out one or more of the following steps:

(i) changing a precursor group $R^{3'}$ to a group R^3 or a group R^3 to a different such group;

(ii) removing any protecting group from $R^{2'}$.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PHM 70470/WO

Box No. I TITLE OF INVENTION

CHEMICAL COMPOUNDS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

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☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet should not be included in the request.

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- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

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State *(that is, country)* of residence: GB

This person is applicant for the purposes of:

- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:

- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:

- [ ] all designated States
- [ ] all designated States except the United States of America
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This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:

- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] AL Albania .....
- [X] AM Armenia .....
- [X] AT Austria .....
- [X] AU Australia .....
- [X] AZ Azerbaijan
- [X] BA Bosnia and Herzegovina .....
- [X] BB Barbados
- [X] BG Bulgaria .....
- [X] BR Brazil .....
- [X] BY Belarus .....
- [X] CA Canada
- [X] CH and LI Switzerland and Liechtenstein
- [X] CN China .....
- [X] CU Cuba .....
- [X] CZ Czech Republic .....
- [X] DE Germany .....
- [X] DK Denmark .....
- [X] EE Estonia .....
- [X] ES Spain .....
- [X] FI Finland .....
- [X] GB United Kingdom
- [X] GD Grenada
- [X] GE Georgia .....
- [X] GH Ghana .....
- [X] GM Gambia
- [X] HR Croatia .....
- [X] HU Hungary .....
- [X] ID Indonesia
- [X] IL Israel .....
- [X] IN India .....
- [X] IS Iceland
- [X] JP Japan .....
- [X] KE Kenya .....
- [X] KG Kyrgyzstan .....
- [X] KP Democratic People's Republic of Korea .....
- [X] KR Republic of Korea .....
- [X] KZ Kazakhstan .....
- [X] LC Saint Lucia
- [X] LK Sri Lanka
- [X] LR Liberia
- [X] LS Lesotho .....
- [X] LT Lithuania
- [X] LU Luxembourg
- [X] LV Latvia
- [X] MD Republic of Moldova .....
- [X] MG Madagascar .....
- [X] MK The former Yugoslav Republic of Macedonia .....
- [X] MN Mongolia
- [X] MW Malawi .....
- [X] MX Mexico .....
- [X] NO Norway
- [X] NZ New Zealand .....
- [X] PL Poland .....
- [X] PT Portugal .....
- [X] RO Romania
- [X] RU Russian Federation .....
- [X] SD Sudan
- [X] SE Sweden
- [X] SG Singapore
- [X] SI Slovenia .....
- [X] SK Slovakia .....
- [X] SL Sierra Leone
- [X] TJ Tajikistan .....
- [X] TM Turkmenistan .....
- [X] TR Turkey .....
- [X] TT Trinidad and Tobago .....
- [X] UA Ukraine .....
- [X] UG Uganda .....
- [X] US United States of America .....
- [X] UZ Uzbekistan .....
- [X] VN Viet Nam .....
- [X] YU Yugoslavia .....
- [X] ZW Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- [X] DM DOMINICA [X] ZA SOUTH AFRICA .....
- [X] UE UNITED ARAB EMIRATES [X] TZ TANZANIA .....
- [X] CR COSTA RICA [X] MA MOROCCO .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box N . VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 05 Feb 99 (05.02.99)	9902455.6	GB		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): item (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 4
description (excluding sequence listing part)	: 66
claims	: 4
abstract	: 1
drawings	:
sequence listing part of description	:
Total number of sheets	: 75

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract: I

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

T. Bryant

BRYANT, Tracey
AGENT FOR APPLICANT

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rul s 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable; item 5 below.	
PHM 70470/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/00284	31/01/2000	05/02/1999
Applicant		
ZENECA LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] it is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   INDOLE DERIVATIVES AS ANTI-INFLAMMATION AGENTS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

Interna[redacted]plication No
PCT/GB 00/00284

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/42 C07D405/12 C07D413/12 C07D403/12 C07D409/12
A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Y. YOKOYAMA ET. AL.: "New Synthetic Method for Dehydrotryptophan Derivatives. Synthetic Studies on Indoles and Related Compounds. XXXIV." CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 42, no. 4, 1994, pages 832-8, XP000887306 page 834, compound 18d; page 835, compound 9b ---	9
X	Y. MURAKAMI ET. AL.: "Direct Regioselective Vinylation of Indoles Using Palladium (II) Chloride." HETEROCYCLES, vol. 22, no. 7, 1984, pages 1493-6, XP000909376 page 1494, compound 3c; page 1495, compound 6. --- -/--	9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2000	30. 08. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Helps, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 186 367 A (WARNER-LAMBERT) 2 July 1986 (1986-07-02) claims; examples	1-10
A	US 5 399 699 A (KOLASA ET. AL.) 21 March 1995 (1995-03-21) Scheme 4, compounds 22-24	1-10
A	US 5 482 960 A (BERRYMAN ET. AL.) 9 January 1996 (1996-01-09) column 1, line 1 - line 22; claims; examples	1-10
A	P. ROSENMUND ET.AL.: "Decarboxylierungen einiger 1-Alkyl-2-carboxy-3-indolessigsäuren sowie Synthese eines 5-Thiocyanato-2,3-dihydroindols." CHEMISCHE BERICHTE, vol. 108, 1975, pages 3538-42, XP000909395 page 3539, compound 2d	1-10
A	R. TROSCHÜTZ ET. AL.: "Synthesis of Substituted 3-Amino-4-Cyano-1-oxo-1,2,5,10-tetrahydroazepino[3,4-b]indoles." JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 34, 1997, pages 1431-40, XP000909451 page 1439, column 1, paragraph 4	1-10
P,X	WO 99 07678 A (ZENECA) 18 February 1999 (1999-02-18) cited in the application page 1, line 1 - line 30; claims; examples	1-10
P,X	WO 99 07351 A (ZENECA) 18 February 1999 (1999-02-18) cited in the application claims; examples	1-10
P,X	WO 99 33800 A (HOECHST) 8 July 1999 (1999-07-08) claims; examples	1-10

INTERNATIONAL SEARCH REPORT

In [redacted]nal application No.
PCT/GB 00/00284

Box I Observations wher c rtain claims were found unsearchable (Continuation of item 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 9

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-9

Second medical use of known pharmaceutically active compounds, as well as first medical use of a subset of said compounds, and new compounds per se.

2. Claim : 10

Process of preparation of known compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[illegible]pplication No
PCT/GB 00/00284

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 186367 A	02-07-1986	US 4675332 A	23-06-1987
		AT 86252 T	15-03-1993
		AU 576131 B	11-08-1988
		AU 5050885 A	19-06-1986
		CA 1259317 A	12-09-1989
		CN 1005974 B	06-12-1989
		DE 3587148 A	08-04-1993
		DE 3587148 T	15-07-1993
		DK 568885 A	11-06-1986
		ES 549768 D	16-04-1986
		ES 8700252 A	01-01-1987
		FI 854821 A,B,	11-06-1986
		GR 852948 A	11-04-1986
		IE 58554 B	06-10-1993
		JP 1925657 C	25-04-1995
		JP 6053736 B	20-07-1994
		JP 61191683 A	26-08-1986
		KR 8900292 B	13-03-1989
		NO 854941 A,B,	11-06-1986
		NZ 214480 A	30-05-1988
		PH 24075 A	05-03-1990
		PT 81637 A,B	01-01-1986
		ZA 8508651 A	24-06-1987
US 5399699 A	21-03-1995	ZA 9500555 A	06-02-1996
US 5482960 A	09-01-1996	CA 2202051 A	23-05-1996
		EP 0790993 A	27-08-1997
		JP 10508843 T	02-09-1998
		WO 9615125 A	23-05-1996
WO 9907678 A	18-02-1999	AU 8638098 A	01-03-1999
		EP 1001935 A	24-05-2000
		NO 20000572 A	04-04-2000
		ZA 9807087 A	08-02-1999
WO 9907351 A	18-02-1999	AU 8638198 A	01-03-1999
		EP 1003504 A	31-05-2000
		NO 20000573 A	04-02-2000
		ZA 9807090 A	08-02-1999
WO 9933800 A	08-07-1999	AU 2052899 A	19-07-1999

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 September 2000 (11.09.00)	
International application No. PCT/GB00/00284	**Applicant's or agent's file reference** PHM 70470/WO
International filing date (day/month/year) 31 January 2000 (31.01.00)	**Priority date** (day/month/year) 05 February 1999 (05.02.99)
Applicant FAULL, Alan, Wellington et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

21 August 2000 (21.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year) 11 August 2000 (11.08.00)	
Applicant's or agent's file reference PHM 70470/WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/00284	**International filing date** (day/month/year) 31 January 2000 (31.01.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ASTRAZENECA UK LIMITED 15 Stanhope Gate London W1Y 6LN United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address	State of Nationality	State of Residence
ASTRAZENECA AB S-151 85 Södertälje Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Dominique DELMAS
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

TENT COOPERATION TREA Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year) 11 August 2000 (11.08.00)	
Applicant's or agent's file reference PHM 70470/WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/00284	**International filing date** (day/month/year) 31 January 2000 (31.01.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

BRYANT, Tracey
Global Intellectual Property
AstraZeneca UK Limited
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
United Kingdom

State of Nationality:

State of Residence:

Telephone No.: 01625 513228

Facsimile No.: 01625 583358

Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
United Kingdom

State of Nationality:

State of Residence:

Telephone No.: 01625 513228

Facsimile No.: 01625 583358

Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Dominique DELMAS Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PHM 70470/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00284	31/01/2000	05/02/1999
International Patent Classification (IPC) or national classification and IPC		
C07D209/42		
Applicant		
ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/08/2000	30.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Helps, I Telephone No. +49 89 2399 8209

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00284

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-66 as originally filed

Claims, No.:

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 10.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	9
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	9
Industrial applicability (IA)	Yes:	Claims	1-6,8,9

No: Claims 7 see below

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

V. CITATIONS AND EXPLANATIONS

The following documents are cited in this report.

Chemical and Pharmaceutical Bulletin, vol. 42, p.832-8 (1994)	(A)
Heterocycles, vol. 22, p.1493-6 (1984)	(B)
EP-A-0,186,367	(C)
WO-A-99 07678	(D)
WO-A-99 07351	(E)
WO-A-99 33800	(F)

Document (A) discloses the compound 1-benzyl-2-ethoxycarbonyl- 3-(2-acylamino-2-methoxycarbonylethenyl)-indole (see page 834, compound no. 18d). This compound is novelty destroying for claim 9 in which R1 is phenyl, X is CH2, R2 is COOEt, R3 is ethenyl substituted by NHCOCH3 and COOCH3 and R4-R7 are hydrogen.

Document (B) discloses the compound 1-benzyl-2-ethoxycarbonyl-3-(2-ethoxycarbonylethenyl)-indole (see page 1494, compound 3c). Also, the compound 1-benzyl-2-ethoxyarbonyl-3-(2-cyanoethenyl) indole is disclosed on page 1495 (see compound 6). These compounds are novelty destroying for claim 9 in which R1 is phenyl, X is CH2, R2 is COOEt, and R3 is cyano or methoxycarbonyl substituted ethenyl.

Claim 9 therefore does not meet the novelty requirements of Article 33(2) PCT.

Claim 1 is rendered novel by the new medical use of the compounds described therein as inhibitors of MCP-1 or RANTES induced chemotaxis. The dependent claims 2-6 are novel by consequence. Claim 7 is rendered novel by the use of the compounds described therein in therapy. The dependent claim 8 is novel by consequence.

Claims 1-8 therefore meet the Novelty requirements of Article 33(2) PCT.

The closest prior art, Document (C), describes 3-substituted indole-2-carboxylic acids which may be substituted at the 1-position by a benzyl group. these compounds are

useful as antiallergy agents. However, there is no teaching in document (A) to suggest that the compounds described therein could be used for the preparation of medicaments for the treatment of disorders for which a RANTES induced chemotaxis inhibitor or MCP-1 inhibitor is indicated (e.g. inflammatory diseases, restenosis, atherosclerosis, etc.). Inventive step (Article 33(3) PCT) is recognised because the problem of providing compounds for the treatment of disorders associated with RANTES induced chemotaxis or MCP-1 has been solved in a non obvious manner.

For the assessment of the present claim 7 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VII. CERTAIN DEFECTS IN THE INTERNATIONAL APPLICATION.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents (A) to (C) is not mentioned in the description, nor are these documents identified therein.

VIII. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION.

It is noted that definitions such as "optionally substituted alkyl....aryl...heteroaryl" used in claim 1 cover said groups bearing any known organic radical or functional group as substituents, without limitation on size or reactivity. It cannot be predicted that the presence of any known substituent would give rise to a compound active as an MCP-1 inhibitor, because steric effects and non selective binding would be expected to occur with some substituents falling within the scope of the above definition. Also, it is known in pharmaceutical chemistry that small structural changes to heterocyclic rings can lead to considerable changes in a pharmacological activity, or to compounds with a completely different activity. The skilled man would therefore not be able to predict if all compounds falling within the said definition "heteroaryl" would actually solve the problem underlying the present application (i.e. the provision of MCP-1 inhibitors). The

Applicant is requested to take position regarding these observations.

At present no priority document is available. The examination has been carried out assuming that the priority date is validly claimed. If during the subsequent procedure (e.g. EPO examination) the priority date is found to be invalid for some or all of the presently claimed subject matter, the intermediate documents (D)-(F) may be taken into consideration for the evaluation of Novelty and/or inventive step.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRYANT, Tracey
Global Intellectual Property
AstraZeneca UK Limited
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
ROYAUME-UNI

Date of mailing (day/month/year)
08 May 2000 (08.05.00)

Applicant's or agent's file reference
PHM 70470/WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/00284

International filing date (day/month/year)
31 January 2000 (31.01.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ZENECA LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
C. CARRIÉ
Christine Carrié
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year)	
11 August 2000 (11.08.00)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
PHM 70470/WO	
International application No.	**International filing date (day/month/year)**
PCT/GB00/00284	31 January 2000 (31.01.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ASTRAZENECA UK LIMITED 15 Stanhope Gate London W1Y 6LN United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address	State of Nationality	State of Residence
ASTRAZENECA AB S-151 85 Södertälje Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Dominique DELMAS
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38